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STUDIES ON THE INHALATION TOXICITY OF DYES PRESENT IN COLORED SMOKE MUNITIONS FINAL REPORT FOR PHASE IV STUDIES. 90-DAY INHALATION EXPOSURES OF RATS TO DYE AFROSOLS

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respirable particle size range (2.1-4.2 µm mass median aerodynamic diameter) for 6 hr/day, 5 days/week for a period of 90 days. The objective was to determine an exposure concentration that produced no observable adverse effects. Nominal exposure concentrations selected for both dye exposures were 0, 1, 10, and 100 mg/m³. Actual concentrations were within 10 of these nominal

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EXECUTIVE SUMMARY

The U.S. Army has an interest in the potential inhalation toxicity of a yellow dye (SY) and a yellow/green dye mixture (SY/SG) used in colored smoke munitions. The chemical name of the major component of the yellow dye is 2-(2'quinolinyi)-1,3-indandione (QI) (C.I. Solvent Yellow 33, C.I. 47000) and the major component of the green dye is 1.4-di-p-toluidinoanthraquinone (TA) (C.I. Solvent Green 3, C.I. 61565). SY contains only QI, while the SY/SG dye mixture contains 30 percent QI and 70 percent TA. To test the inhalation toxicity of these materials, exposure atmospheres of SY or SY/SG were generated in a respirable particle size range and used for inhalation exposures of F344 rats at three concentrations for 6 hr/day, 5 days/week for a period of 90 days. The purpose of these studies was to find a no-observable-adverse-effect level for each dye material. Animals were observed for signs of toxicity at the end of each exposure and after a 30-day post-exposure recovery period. For these studies, the biological indicators of toxicity were gross clinical observations, changes in body weight gain, respiratory function measurements, biochemical and cellular analyses of bronchoalveolar lavage fluid, lung tissue enzyme and connective tissue biochemistry, blood and serum chemistries, and histopathology of selected tissues. This report describes the results of these investigations.

In the 90-day inhalation exposure to SY dye, rats were exposed to aerosols of SY dye at average concentrations of 1.0 \pm 0.2, 10.8 \pm 1.8 or 100 \pm 17 mg/m³ (\bar{X} \pm SD). The average particle size of these aerosols ranged from 2.1 to 4.0 μ m (mass median aerodynamic diameter) with the higher exposure concentrations having the larger particle size. The geometric standard

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deviation (σ_{α}) of all dye aerosols was approximately 2.0. After exposures, it was found that very little SY dye (QI) was retained in the lungs, indicating the SY dye was rapidly cleared. Exposure-related histopathological lesions consisted of the accumulation of foamy alveolar macrophages in lungs of rats exposed to the highest concentration of SY dye. Pigments, probably metabolites of quinoline dye, were present in the nasal cavity. liver and kidneys. Lesser deposits of pigments were seen in the medium exposure concentration group. No reaction was seen to these deposits and they were not considered an adverse effect. The body weights of the animals exposed to the highest concentration averaged 4 percent less than controls (p < 0.05) at the end of the exposure, but returned to control values after the 30-day recovery period. Except for these differences, no other toxicologically significant effects were seen.

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Rats were exposed to aerosols of SY/SG dye mixture having average concentrations of 1.1 \pm 0.5, 10.2 \pm 3.1 or 101 \pm 23 mg/m³ (\bar{X} \pm SD). The average particle size of these aerosols ranged from 2.8 to 4.2 µm (mass median aerodynamic diameter) with a σ_{α} of approximately 2.0. As with the studies on SY dye exposures, it was found that the QI component of the SY/SG dye mixture cleared from lungs at a very rapid rate. However, the SG portion of the SY/SG dye mixture was retained in lungs for a much longer time. Rats exposed to the highest concentration of SY/SG dye mixture had a significantly lower body weight after the 90-day exposures than controls, approximately 7 percent less. Analysis of bronchoalveolar lavage fluid showed an influx of neutrophils and increased enzyme activities, indicating that a mild pulmonary inflammatory response occurred in high level SY/SG exposed rats.

II pulmonary epithelial cell hyperplasia and proliferation of foamy alveolar macrophages and lymphoid hyperplasia in the tracheobronchial lymph nodes of rats exposed to the highest concentration of SY/SG dye. This mild response was also seen in some of the medium dose animals, but no lesions were observed in the low dose animals. No other adverse effects were observed.

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Pigments, probably metabolites of quinoline dye, were found in the nasal cavity, liver and kidneys of the high and medium exposure groups. This pigment deposition was not considered an adverse effect.

In summary, minimal histopathological lesions were observed in rats exposed to up to $100~\text{mg/m}^3$ of SY dye for 65 days over a 90-day period. In rats exposed to the SY/SG dye mixture, an exposure concentration of $10~\text{mg/m}^3$ was sufficient to induce some histopathological lesions in the lung. Thus, the no-observable- adverse effects level of SY was $10~\text{mg/m}^3$, and for SY/SG it was $1~\text{mg/m}^3$ under the above exposure conditions. It is apparent that the SY/SG dye mixture was more toxic to the lung than is the SY dye. This is at least partially due to the longer retention time in the lung for the SG portion of the dye mixture as compared to the SY.

PREFACE

The authors acknowledge the outstanding contributions of all members of the Inhalation Toxicology Research Institute, without whose help these studies could not have been completed. Histopathological examination of tissues was performed at Experimental Pathology Laboratories, Inc., Herndon, Virginia, by Dr. Deborah Banas, Diplomate ACVP. In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Users of Laboratory Animals." prepared by the Committee on the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (OHEW Publication No. (NIH) 80-23, Revised 1980). This research was conducted in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care. This research was conducted in accordance with the Good Laboratory Practice Regulations for Nonclinical Laboratory Studies (FDA, 1978). These studies were inspected by the ITRI Quality Assurance Unit, and the results in the final report were audited for completeness and accuracy of reporting to the raw data. This final report is in accordance to the experimental methods described in study protocols and standard operating procedures. This research was supported by the U. S. Army Medical Research and Development Command under a Memorandum of Understanding Agreement No. AT(29-2)-2138/3807 with the Lovelace Inhalation Toxicology Research Institute, which is operated for the U.S. Department of Energy under DOE Contract No. DE-ACO4-76EV01013.

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INTRODUCTION

The U.S. Army needs to obtain information on the inhalation toxicity of the dyes present in colored smoke munitions. The major concern is for the health of munition production workers who could be exposed to fine dusts containing the dyes during production of the smoke munition. In the project, *Studies on the Inhalation Toxicity of Dyes Present in Colored Smoke Munitions (Project Order No. 83PP3807), the Lovelace Inhalation Toxicology Research Institute (ITRI) studied the inhalation toxicity of two dye materials: a yellow dye (SY) and and yellow/green dye mix (SY/SG). The chemical name of the yellow due is 2-(2'-quinolinyl)-1.3-indandions (QI). Various synonyms used for the dye include C.I. solvent yellow 33, C.I. 47000 and D & C yellow No. 11. The green dye is 1.4-di-p-to uidinanthraguinone (TA) and is also called C.I. solvent green 3, C.I. 61565 and D & C Green No. 6. The yellow/green dye mix contains approximately 30 percent yellow due and 70 percent green due. The smoke munitions contain 42 percent by mass of the dyes. The balance of the munition's mass is composed of potassium chlorate, magnesium carbonate and sucrose.

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The work was conducted in four phases. Phase I included standardization of methods for generation of aerosols of the test materials and the physical/chemical characterization of the aerosols. Phase II consisted of range-finding experiments to determine acute toxic effects from exposure to high concentrations of the dyes and to select exposure concentrations for the next two phases of the study. In Phase III, four-week exposures of animals to varying concentrations of the dyes were used to determine the lowest exposure concentration that will produce pathological changes. Phase IV was a 90-day

subchronic study to determine a no-observable-adverse effects level (NOAEL) of exposure.

This is a final report of the work completed in Phase IV of these studies.

90-DAY INHALATION EXPOSURE TO SY DYE

Nominal exposure concentrations selected for this study were 0, 1, 10, and 100 mg/m³ given for 6 hours/day, 5 days/week, for a period of 90 days. These concentrations were selected on the basis of the results from the 4-week exposures to SY dye (Phase III). The highest level was selected as a concentration expected to produce minimal toxic responses. The lowest level was selected as the lowest concentration that could be consistently maintained. The middle level was selected as a concentration that differs by a factor of 10 from the low and high levels.

Statistical Analyses

Where possible, computer software packages such as BMDP, RS1 or Path/Tox were used for data handling and analysis. Standard tests applied to the experimental data were one-way analyses of variance followed by tests for the equality of means, such as simple t-tests or multiple comparison t-tests. Usually a confidence level of 0.05 was used, although in some cases significance was expressed in much smaller or much larger values.

Chemicals

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SY was supplied by the U. S. Army Medical Bioengineering Research and Development Laboratory (Fort Detrick, Frederick, MD). The purity of this dye material (QI) was 93 percent and was used without further purification.

<u>Animals</u>

Male and female Fischer-344 (F344/N) rats, 15-20 weeks of age were used for this study. The rats were obtained from an existing colony at the Inhalation Toxicology Research Institute. Disease surveillance monitoring of the rat breeding colony is conducted at quarterly intervals. Thirty weanling

F344 rats (15 males, 15 females) are assigned to one of 23 available rat housing rooms. Room assignments are made from a randomized list of animal rooms. Of the thirty animals assigned to a room, 10 (5 of each sex) are sacrificed for surveillance at 3 months of age, 10 at one year of age, and 10 at 2 years of age. This system results in 3 age groups and 3 animal rooms being surveyed every 3 months. The animals are anesthetized and blood is collected prior to sacrifice. The serum is diluted, heat-inactivated and submitted to Microbiological Associates (Bethesda, MD) for serologic testing for Sendai virus, rat corona-virus/Sialodacryodenitis virus (RCV/SDAV). Reovirus type 3 (Reo 3), Theiler's encephalomyelitis virus (GD VII), Toolan's H-1 virus (H-1), Kilham rat virus (KRV), Lymphocytic choriomeningitis (LCM) and Mycoplasma pulmonis. Bacterial cultures are also performed on swabs or tissue samples from the masal cavity, lung, spleen, liver, kidney and cecum. Media have been selected to identify the major bacterial pathogens of rodents. Following collection of samples for bacterial culture, a complete necropsy is performed. Tissues from all major organs and any gross lesions are collected and processed for histopathology. During the necrospy, the skin is examined grossly for signs of ectoparasites, skin scrapings are taken if indicated, and a section of skin is processed for histopathology. Fecal material and/or cecal contents are examined for internal parasites by fecal floatation.

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At the age for experimental use, rats were moved to Hazleton 2000 exposure chambers for at least 3 weeks before exposures to acclimate them to that environment and to ascertain their physical well being. Rats were assigned to experimental groups by a randomization program on the Path/Tox computer system (Xybion Medical Systems Corp., Cedar Knolls, NJ) according to

body weight. Rats were uniquely identified using ear tags. During these studies all animals were given food (Wayne Lab Blox) and water <u>ad libitum</u> except that food was withheld during exposure periods.

Inhalation exposure chambers were maintained at $75 \pm 3^{\circ}f$ and 35-70 percent relative humidity. This temperature above that normally found in an animal room ($72 \pm 2^{\circ}f$) in order to compens for body heat loss due to chamber airflow. Chamber airflow rate, temperature, humidity, and pressure relative to the room were monitored throughout this study. Temperature and humidity measuring devices were calibrated and checked before initiation of the study. At the time of sacrifice rats were euthanized by intraperitoneal injections of T-61 euthanasia solution.

Animal Exposures

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Aerosols of SY dye material were generated using a Jet-O-Mizer air jet mill as previously described. 3,4 Four Hazleton 2000 chambers (Hazleton Systems, Inc., Aberdeen, MD) containing 6 tiers of animal cages (10-16 rats per tier) were used for these whole-body inhalation exposure studies. For these studies, 392 rats (196 males and 196 females) were entered into each exposure chamber in four groups (1 control and 3 treated groups). Immediately after the last day of exposures, a portion of the animals (132 males and 132 females) were taken for toxicological evaluations, while the remaining animals from each of the four exposure groups were held for 30 days to determine if animals could recover from any exposure-related toxic responses.

The SY exposure concentration was determined gravimetrically from filter samples taken daily from each exposure chamber. Particle size of the dye material was measured using a Lovelace Multi-Jet cascade impactor. These particle size measurements were taken each day during the first week of

exposure and then at the intervals shown in Table 1. Concentration and size characteristics of the exposure atmospheres for each exposure chamber for each exposure day are shown in Table 1. The daily concentrations were 1.0 \pm 0.2, 10.8 \pm 1.8 and 100 \pm 17 mg/m³ (\bar{X} \pm SD). The coefficient of variation of daily aerosol concentrations was between 17 and 20 percent.

Clinical Observations

Detailed clinical observations were performed on all animals before exposures to ensure that they were in good health. Detailed clinical observations were also done twice daily throughout the exposure period and during the 30-day recovery period. The animals were also observed twice daily for morbidity and mortality. No clinical abnormalities were noticed and all animals survived to sacrifice times.

Animal Body Weights

During the 90-day exposures, a subset of both male and female rats (n = 20 per sex) from each exposure chamber (including the control chamber) were weighed on a weekly basis. This same subset of animals were held for the 30-day recovery time and also weighed at the end of this recovery period. Body weights measured throughout the study are summarized in Table 2. Before exposures, animal weights did not differ among the different exposure groups. However, after exposures rats exposed to the highest level of SY dye (100 mg/m 3) gained weight at a slightly slower rate than controls. At the end of exposures, these high level exposed rats weighed approximately 4 percent less than the control animals (for the null hypothesis P < 0.05 in Dunnett's multiple comparisons procedure). During the 30-day post-exposure recovery period, the weights of male rats exposed to the highest level of SY dye returned to control male animal weight values, whereas the body weights of

Table 1

SY Aerosol Concentration and Size Characteristics for the 90-Day Inhalation Study

	LOW			M	MEDIUM			HIGH			
	Conc	MMA	.0 ^a	Conc.	MMA	0	Conc.	MM	AD		
	(mg /	(nw)	og b	(mg/m ³)	(mm)	<u>_a</u>	(mg/m ³)	(mm)	°g_		
Day 1	1.7	2.3	2.0	14.5	2.5	1.9	76	3.5	1.9		
2	0.7	2.2	2.0	7.4	2.7	2.0	52	3.8	1.8		
3	0.8	2.2	2.0	10.1	2.9	2.0	100	4.4	2.0		
4	1.0	2.2	2.0	10.2	2.8	2.0	107	4.4	2.1		
5	1.1	2.1	2.0	10.8	2.6	2.0	112	4.4	1.9		
6	1.1			8.6			126				
7	1.0	2.3	2.4	13.1	2.6	2.0	89	4.1	1.9		
8	1.1			11.7			98				
9	1.3			10.7			115				
10	0.9			10.9			87				
11	1.1	2.1	1.9	12.1	2.8	1.9	102	3.3	1.8		
12	1.1	• • • • • • • • • • • • • • • • • • • •		11.4			85				
13	0.9			12.2			95				
14	0.6			12.4			104				
15	1.3			16.6			151				
16	0.6	2.0	1.9	13.8	2.8	1.9	86	4.0	1.8		
17	0.9	2.0	1.3	13.2	ι.υ	1.7	108	7.0			
18	1.0			16.3			133				
19	1.1			9.8			108				
20	0.7			10.4			78				
21	1.1			10.4			64				
22	1.1	2.1	1.9	10.1	2.9	2.0	98	4.3	1.9		
23	1.1	2.1	1.3	11.0	2.3	2.0	122	4.5	1.3		
23 24	0.9			9.4			90				
25	1.2			8.9			97				
	0.9			8.1			95				
26	0.9	2.1	1.8	12.0	2.9	2.0	115	4.5	1.9		
27		2.1	1.0	12.0	6.7	2.0	86	4.5	1.3		
28 29	0.8			13.5			91				
	1.1			9.4			100				
30	1.1						103				
31	1.3			12.7			103				
32	1.5			12.4	2.0	2.0			2.0		
33	1.0	2.0	2.0	10.9	2.8	2.0	95	4.4	2.0		
34	1.1			8.9			96				
35	1.4			9.0			113				
36	1.0			9.6			94				
37	1.1			10.7			96				
38	1.0	2.0	1.9	9.8	2.5	2.0	78	3.7	2.2		
39	0.9			9.9			78				

Table 1 (Continued)

	LOW			M	EDIUM		HIGH		
	Conc.	MM	AD ^a	Conc.	MM.	AD	Conc.	M	IAD
	(mg/m ³)	(mm)	<u> </u>	(mg/m ³)	(mm)	<u> 9</u>	(mg/m^3)	(my)	<u> </u>
Day 40	1.2 1.3			10.7			94		
41	1.3			10.3			103		
42	1.3			11.5			71		
43	0.9	2.0	2.1	9.6	3.2	2.0	66	3.7	2.0
44	1.1			12.8			120		
45	1.2			10.8			109		
46	0.9			10.0			96		
47	0.9			10.8			97		
48	0.9	2.1	1.9	10.5	3.1	1.9	90	3.9	2.0
49	1.1			10.3			98		
50	0.8			9.6			99		
51	1.3			9.8			100		
52	1.2			10.8			105		
53	1.2			12.2	3.6	2.7	113	3.6	1.8
54	1.0	2.1	2.2	12.5	• • •		135		
55	0.9	• • •	• • •	8.1			103		
56	0.8			10.4			117		
57	0.9			9.4			96		
58	1.1	2.3	2.2	9.8	2.8	2.1	112	4.2	2.1
59	1.0			8.7			129	• • • •	• • •
60	1.1			10.5			115		
61	0.9			10.3			100		
62	0.9	2.1	2.1	10.8	3.1	2.1	82	3.4	2.0
63	0.9	• • •		7.2	• • •	• • • • • • • • • • • • • • • • • • • •	98	• • •	•
64	0.9			8.5			105		
65	1.0			9.7			122		
X SD	1.0	2.1	2.0	10.8	2.9	2.0	100	4.0	2.0
SD	<u>+</u> 0.2	<u>+</u> 0.1	<u>+</u> 0.1	<u>+</u> 1.8	<u>+</u> 0.3	<u>+</u> 0.1	<u>+</u> 17	±0.4	<u>+</u> 0.1

Daily chamber concentrations were determined by the mean of 3 two-hour samples taken during the day.

 $^{^{}a}$ MMAD = mass median aerodynamic diameter b $_{\sigma g}$ = geometric standard deviation

Weekly Average Weights^a of Male and Female Rats for the 1000円の資金を含 Table 2 | 100mm | 10

90-Day SY Inhalation Exposure Study

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- 1		<u> </u>	= +	+1	+1	+1	+1	+1	+1	+1	+1	+1	+ 1	+1	+i	+1
	ຕຼີ	Female	203	203	215	20	90.	20	503	212	Ξ	214	113	113	=======================================	220
를	J	, '	()				•		•••		•••	•••	•		••	•
Ξ	(100 mg/m ³)	1	~	_	_	ω.	<u>م</u> .	<u>.</u> .	<u>۾</u> .	٠,	<u>.</u> م	۾ .	۾ .		مر	6 0
	Ē	Male	4	327 ± 14	4	=		=	=	<u>-</u>	2.	~	=	1 2	-	± 18
		E E	0	<u>~</u>	22	مِ	=	25	5	7	2	6	7		2	399
,	l	1	32	35	ë	36	36	3	36	36	36	36	3	3	31	3
ı	ì	.1	0	6	7	2	_	0	0	4	6	0	6	6	0	0
		Female	203 ± 10	+1	+1	+1	+1	+1	+	+1	+1	+1	+1	+1	+1	+1
	E E	Fell	03	05	19	Ξ	12	10	15	12	11	23	25	22	20	56
£	7	, 1	5	2	2	2	2	2	7	~	2	8	2	7	2	2
Medium	(10.8 mg/m^3)	ı	=	2	50	4	4	91	4	91	15	6	91	51	81	11
	=	Male	+1	+ 20	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	388 + 18	+1
		=	18	23	133	899	69	69	111	378	382	88	193	360	888	110
,		'	(-)	(-)	(-)		(-)	()	(-)	()	(-)	(-)	(,,	(-)	(-,	
		انه	320 ± 38 203 ± 10 3	+ 13	12		6	20	216 ± 9	80	89	7 +	_	7	8	10 +
	_	<u>a</u>	+1	+1	+1		+1	+1	+1	+1	+1	+1		+1		+1
	~E	E .	203	202	216	6d	216	215	216	221	217	223	227	224	211	223
1 0	٤	•				ain										
	0.6	1	38	324 ± 19	24	obt	19	17	9	91	15	35	15	9(393 ± 13	18
	~	a e	+1	+1	+1	ņ	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1
		Ĭ	320	324	330	č	375	376	383	384	389	397	405	405	393	406
	•	•		•		ght	•				• •		•	•	•	
	1	ابه	15	د +۱	91	weights not obtained	10	20	6	œ	80	~	+1	80	20	10
		ma le	+1	+1	+1	P	+;	+1	+1	+1	+1	+1	+1	+1	+1	÷I
ē		Fen	204	203	217	Val	214	212	216	219	219	224	228	225	223	228
Control		•														
S		j	39	56	24		17	19	20	15	+ 13	± 15	+ 18	81 + 1	18	9(
		Ma le	+1	+1	+1		+1	+1	+1	+1	+1	+1	+1		+1	4 1
		X.	322	327 ± 26	342		369	369	376 ± 20	384	386	392	394	397	392	408
	•	•		•	_				_		_	_	_		_	
			ن.	.,	(*)	4	٠,	¥	,-	w	J,	7	=	12		~
			Week													

dAverage animal weight (grams) \pm 50, n = 20. bShown to be significantly lower than the control group of the same week interval using Dunnett's multiple comparisons at P \leq 0.05.

female rats exposed to the highest level of SY dye remained significantly lower than control female body weights.

Lung Content of QI After Exposure to SY Dye

On the day after the last exposure day, lungs from six rats (three male and three female) from each chamber (low, medium and high concentration) were analyzed for QI content. Animals were sacrificed and lungs removed, with care to avoid contamination with yellow dye on the pelt. Each lung was homogenized in 1.5 mL of acetonitrile and centrifuged, and the supernatant was removed. The pellet was resuspended in 2 mL acetonitrile, centrifuged, and the supernatant removed. This procedure was repeated three more times. Preliminary experiments in which excised control lung lobes were directly injected with a syringe with a known amount of SY dye dissolved in acetonitrile prior to homogenization showed that this extraction procedure removed 94 percent of the QI. The combined supernatants were diluted to 10 mL and analyzed for QI by HPLC using the following conditions:

- -- reverse phase column (Alltech C-18, 10μ ; 25 cm x 4.6 mm)
- -- 9:1 acetonitrile:water mobile phase (1 mL/min)
- -- UV detection at 435 nm

The results, shown in Table 3, demonstrate that very little QI was retained in the lung. Thus, the majority of the QI deposited in lungs during exposures was cleared at a rapid rate. Assuming 10 percent pulmonary deposition of inhaled SY dye aerosol⁵ and a minute volume of 200 mL/min, 720 μ g of SY dye/day should have been deposited in animals exposed to the high concentration. Of the amount calculated to be deposited during only the last day of exposure, only ~ 0.2 percent remained 16 hours after exposure. This finding is similar to the results found in the four-week exposure of rats to SY dye aerosols (Phase III). \frac{1}{2}

Table 3
Lung Burden of QI After a 90-Day Exposure to SY Dye

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	Aerosol Concentration	Lung Burden Mean <u>+</u> SE (n = 3)
	(mq/m^3)	(µg/lung)
<u>Male</u>	1	0.050 ± 0.030
	10	0.20 ± 0.10
	100	1.3 <u>+</u> 0.3
<u>Female</u>	1	0.025 <u>+</u> 0.007
	10	0.10 ± 0.04
	100	1.3 + 0.2

Respiratory Function

The respiratory function of 8 male rats and 8 female rats at each exposure level (control, low, medium and high) was measured before exposures began, at the end of the 90-day exposures and at 30 days after the end of exposures, using methods previously published. Each rat was anesthetized with halothane in air, intubated with orotracheal and esophageal catheters and placed prone in a plethysmograph. Breathing patterns and dynamic lung mechanics were measured during spontaneous breathing. Prior to each subsequent test procedure, the rat was hyperinflated manually to +20 cm H₂O transpulmonary pressure to stimulate pulmonary stretch receptors, and the various inflation-deflation cycles were performed during the ensuing periods of apnea. The rat resumed spontaneous respiration between each procedure and its anesthetic depth and breathing pattern were stabilized. Measurements included all physiologic subdivisions of lung volume, quasistatic (slow) pressure-volume relationships, carbon monoxide (CO) diffusing capacity, forced exhalation and single-breath N₂ washout. Thirty-seven variables were measured or calculated for each rat, providing information on various aspects of lung respiratory function: ventilation, lung mechanics, gas distribution and gas exchange.

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All data were summarized by measurement period and exposure group. The group data were compared at each measurement time using analysis of variance (BMDP Statistical Software, University of California, Los Angeles). Values for each exposed group were compared to those of the controls by the Student's t-test adjusted for multiple comparisons using the Bonferroni inequality. The criterion for statistical significance was set at the 95 percent confidence level for all comparisons.

The results are summarized in Tables 4 (pre-exposure), 5 (immediately after exposure) and 6 (30 days after exposure). Mean values different from control means at the 95 percent confidence level are indicated in the tables with an asterisk. There were no significant differences among the groups before exposure (Table 4). At the end of exposure (Table 5), the only significant difference was a lower volume-normalized CO diffusing capacity in the high level group as compared to controls. A slightly lower diffusing capacity and slightly higher alveolar volume (measured by gas dilution during the diffusing capacity test) combined to produce the significant difference. At 30 days after the end of exposure (Table 6), the only significant difference was a lower volume-normalized forced expiratory flowrate at 10% of forced vital capacity (i.e., flow rate at low lung volume). As with diffusing capacity, this resulted from nonsignificant differences in the two variables used to calculate the parameter.

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These results indicate very little effect of the 90-day SY dye exposure on respiratory function. Values for single parameters differed significantly between controls and high-level exposed rats after exposure and 30 days later. However, these differences did not comprise a recognizable pattern of physiological change, nor were they supported by trends in related parameters. Thus, in the absence of supportive significant differences or consistent trends, the high exposure level can be considered to have caused no decrement in respiratory function.

TABLE 4
Respiratory Function of Rats Before SY Dye Exposures®

Verteble	Units	Control & SE	38	104 \$ 56	SE	med to	36	High +	×
Body weight	•	592	13	274	9	215	9	214	
Minute volume	84/Kg	331	=	302	2	319	35	2	23
bynamic lang compliance	mt/cm H ₂ 0	0.44	0.05	0.41	0.03	0.43	9.0	0.39	0.03
Quasistatic chord compilance	mt/cm H ₂ 9	0.95	0.03	0.93	0.03	0.99	٥.8	0.97	8.
lotal lang capacity (ILC)	a	15.4	9.9	14.8	0.5	15.3	0.5	15.4	9.5
TLE/body weight	m / / / / / / / / / / / / / / / / / / /	1.09	2.1	55.5	1.9	57.6	2.1	57.7	2.0
Vital capacity (VC)	Ħ	13.2	9.9	12.7	0.5	13.3	6.9	13.1	6.5
WC/TLC	A /A	0.08	0.01	9.0	0.01	0.87	0.0	0.85	9.0
Functional residual capacity (FEC)	ť	3.8	0.1	3.4	0.1	3.4	6.1	3.6	0.2
FRECTLE	# /#	0.24	0.01	0.23	0.0	0.22	0.01	0.24	6.0
Residual volume (RV)	ť	2.2	0.2	1.2	0.1	5.0		2.3	6.1
RWATE	# \#	0.15	0.01	0.14	0.0	0.13	0.01	0.15	6.9
CO diffusing capacity (BLCO)	at/hain/wam Hg	0.309	0.024	0.296	0.027	0.289	0.023	0.277	0.022
PLCO/alveolar vofume	milletin/mm Hg/mil	0.021	0.001	0.020	0.001	0.020	0.00	0.019	0.00
Forced wital capacity (FVC)	ť	13.5	9.6	13.2	9.0	13.1	0.1	13.4	0.7
Percent of FVC exhaled in 0.1 sec	percent	2	~	15	~	25	-	•	~
Rean midexpiratory flowrate (MMEF)	# /sec	29	•	29	•	6 5	•	2	•
MANE / FVC	at/sec/at	4.5	0.4	4.5	0.3	4 .6	0.3	3.7	0 .4
Forced expiratory flowrate at					•				
10% of fvc (FEF10)	mt/sec	۲	~	•	~	2	~	15	~
FEF10/FVC	mt/sec/mt	1.5	0.0	7.7	0.1	•:	6.1	.	6.3
Stope of phase 111 of									
single-breath M2 washout	percent N ₂ /mL	0.57	0.02	93.0	90.0	0.62	9.0	0.56	6.3

^{*}There were no significant differences between treated and control groups at P < 0.05.

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TABLE S

Respiratory Function of Rats at the End of 90-Day SY Dye Exposures

Variable	Units	Control ± SE	×	100	SE	Medica	35	Migh ± SE	SE	
Dody weight	•	313	22	305	22	305	2	æ		
Minute volume	# /kg	328	22	314		318	12	305		
Dynamic lang compilance	mt/cm H ₂ 0	3.0	9.0	0.51	9.0	0.50	9.09	0.53		
Quasistatic chord compilance	ML/cm H20	1.18	90.0	1.1	9.0	1.17	0.01	1.15		
Total lung capacity (TLC)	1	11.2	9.0	16.2	9.0	17.3	9.9	16.9		
N.C./body weight	# Ag	36.6	J.8	*	1.1	58.3	1.1	58.7		
Vital capacity (VC)	ť	15.4	.	14.8	9.0	15.1	0.0	15.4		
WC/TLC	M /M	0.90	0.0	0.92	0.0	0.91	0.01	0.91		
Functional residual capacity (FRC)	1	3.4	0.2	3.0	0.2	3.4	0.2	3.3		
FRC/TLC	et /et	0.20	0.0	0.19	0.01	0.20	0.0	0.3		
Residual volume (RV)	¥	 	0.5	7.7	0.2	1.6	0.2	1.7		
RV/TLC	14	0.10	0.01	0.0	0.03	0.0	0.0	0.10		
CO diffusing capacity (DLCO)	at/min/mm Hg	0.306	9.0.0	0.283	0.017	0.284	0.011	0.265		
DLCC/slveolar volume	at/min/mm Hg/mt	0.019	0.001	0.038	0.00	0.018	6.00]	0.017		
Forced vitel capacity (FVC)	ť	16.0	0 .0	15.3	0.0	16.1	0.0	15.9		
Percent of FVC exhaled in 0.1 sec	percent	5	~	63	~	3	~	\$		
Mean midexpiratory flowrate (MME)	mt/sec	6	~	*	•	6	•	2		
MEE/FVC	mt/sec/mt	5.5	0.4	5.3	0.2	9.6	5.6 0.4	5.5	0.5	
forced expiratory flowrate at					.**					
10% of FWC (FEF10)	mL/sec	12	~	2	~	2	-	2		
FEF10/FYC	mt/sec/mt	1.3	0.1	7.7	0.1	1.4	6.1	1.2		
Stope of phase III of										
single-breath M ₂ washout	percent N2/ML	0.45	0.0	0.57	6.0	0.52	9.0	0.52		

*Olfferent from control mean at P < 0.05.

TABLE 6
Respiratory Function of Rats 30 Days After the End of 90-Day SY Dye Exposures

Yerleble	units	Control	×	10v t SE	SE	Medium 1 SE	35	High : 55	×
Body weight	•	317	*	316		319	**	312	₹.
Minute volume	# We	283	2	5 6		308	•	300	2
Bynamic lung compilance	M/cm M20	0.56	\$	0.62		0.61	90.0	\$.0	9.0
Quasistatic chord compliance	ML/cm M20	1.12	8.0	1.13		1.22	0.01	3.8	0.01
Total lung capacity (TLC)	, =	16.2	9.0	16.6		11.11	.	17.6	6.9
TLC/body weight	A. /kg	53.6	2.5	3.		\$7.6	5.0	2.8	5.0
Vital capacity (VC)	1	14.7	0.1	15.2		16.1	0.0	15.9	9 .
WC/TLC		0.90	0.02	0.92		0.91	0.0	0.9	0 .0
Functional residual capacity (FRC)	ı	3.1	0.2	3.1		3.3	0.1	3.4	0.5
צוביוונ	T T	6.20	0.0	0.19		0.19	0.0	8.0	9.0
Residual volume (RV)	s	1.6	0.2	₹.		1.5	0.1	1.1	0.1
מאינוכ	# /#	0.11	0.0	0.0		8.0	6.6	0.10	0.0
CO diffusing capacity (DLCO)	at/ato/mm Hg	0.297	0.011	0.298		0.23	0.019	0.308	120.0
BLCO/alveolar volume	at/bin/mm Hg/mt	0.018	0.001	0.019		0.017	6.00	0.01	9
Forced witel capacity (FVC)	*	15.8	0.7	16.3		17.0	6.9	16.0	•
Percent of FVC exhaled in 0.1 sec	percent	3	~	2		3	~	23	~
Mean midexpiratory flowrate (MMEF)	M/500	2	•	3		8	•	8	~
INCE /FVC	ML/500/ML	5.5	5.9 0.4	8.9	0.5	5.3	0.5	5.3	0.5
Forced expiratory flourate at									
10% of FWC (FEF10)	mt/sec	23	-	2		2	~	2	~
FEF10/FWC	M_/Sec/M	1.5	6.1	1.2			<u>.</u>	£.	-
Slope of phase III of									
single-breath M ₂ washout	percent N ₂ /ML	0.67	90.0	0.61	9.02	0.55	8.0	0.55	5

*Different from control mean at P < 0.05.

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From the results of the 4-week exposure of rats to SY (Phase III), we suggested it was important to look for indications of emphysematous changes in rats exposed to SY for a longer time. In the 90-day exposed rats there was no indication of any development of emphysematous lesions.

Lung Biochemistry

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Lung damage was assessed by the analysis of bronchoalveolar lavage (BAL) fluid. Previous studies have shown this to be a useful method to detect an inflammatory response in lungs following inhalation of toxic materials.⁷

Analysis of BAL fluid was done after 6 weeks as well as after 13 weeks of exposure and at the 17 week time point (30 days after end of exposure). Parameters measured in BAL fluid included total and differential cell counts, lactate dehydrogenase, B-glucuronidase, acid phosphatase and total protein. There was no indication of any inflammatory response in the lung at any time point (Table 7). There was a slight decrease in the number of macrophages recovered from some of the exposed animals. However, the significance of this is unknown since there was no concomitant increase in lysosomal enzymes or in lactate dehydrogenase to indicate that macrophages had been lysed.

Statistical analysis of these data was by analysis of variance followed by Bonferroni pairwise comparisons of means.

Lung tissue and lavage fluid proteinolytic activity were also measured in control rats and rats exposed to SY dye aerosols. The data were compared statistically using the Student's t-test corrected for 3 comparisons. Results showed no differences in these activities between control and exposed rats after the 90-day exposures (Table 8) or after the 30-day recovery period (Table 9).

Pulmonary Response of Rats Exposed to SY for 90 Days

as Observed in Bronchoalveolar Lavage Fluid

 $(\vec{X} \pm SE, n = 12)$

				E	Exposure Concentration (mg/m ³	ت	ncentr	ation		(m)		Ì		
	Sacrifice Week	Control 0	rol		٦- د	1.0		He .	Medium 10.8	_	100	H1gh 100		
Lactate Dehydrogenase, mlU/g	13	420 380 390	+1+1+1	30 30 30	460 380 310	+1+1+1	60 20 20	530 370 330	+1+1+1	80 20 20	490 410 300	+1+1+1	202	
Acid Phosphatase, mIU/g	6 13	8.8 11.7 12.6	+1+1+1	1.1	9.2 12.5 12.2	+1+1+1	1.0 2.4 1.6	12.7 10.3 10.1	+1+1+1	2.7 1.3 1.0	8.6 9.7 10.2	+1+1+1	1.3 0.5	
β-Glucuronidase, mIU/g	6 13 17	1.8 2.5 1.7	+1+1+1	0.2 0.4 0.2	7.1	+1+1+1	0.3 0.4 0.2	2.2 7.1 2.1	+1+1+1	0.4	9	+1+1+1	0.4	
Protein, mg/g	6 13 7.1	1.7	+1+1+1	0.0	7.9 7.8 1.1	+1+1+1	0.0 1.0	2.0 1.5 1.9	+1+1+1	0.2	2.2 1.6 1.1	+1+1+1	0.3 1.0	
Macrophages, 10 ³ cells/g	9 13 71	1040 850 880	+1+1+1	0E 08 06	790 560 680	+!+!+!	00 \$09 \$08	960 570 690	+1+1+1	20 20 20	1000 520 560	+1+1+1	70 50* 40*	
Neutrophils, 10 ³ cells/g	6 51 71	3 28 11	+1+1+	2 11 6	9 8 8	+1+1+1	36	2 ~ 8	+1+1+1	- 4 ru	 60	+1+1+1	29-	

The values were normalized in this manner to take into account the difference in size avalues represent total amounts of material recovered in BAL divided by the wet weight of the lung in g. There was no statistical difference in the mean wet weight of the lungs between the group.

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comparison of the 3 treatment groups.

Dan interim sacrifice was made after 6 weeks of exposure and a second sacrifice was made at the end of the exposure (13 weeks). The 17 week sacrifice was of rats held for 1 month after the exposure to determine if there was recovery from any exposure-related injury. **Values differ from control values, $P \le 0.05$, by Bonferroni pairwise comparison of means. The critical t-value necessary for rejection of the null hypothesis at $P \le 0.05$ was adjusted for of male versus female lung weights.

Table 8 Lung and Lavage Fluid Proteinolytic Activity in Rats Exposed to SY Dye for 90 Days

mg protein released/hr/g lunga

Lung Tissue:	Control	Low	Medium	<u>High</u>
Total Acid Proteinase Cathepsin D ^b Cathepsin B ^C	10.3 ± 1.0 8.1 ± 0.8 2.2 ± 0.5	9.9 ± 1.3 8.4 ± 0.8 1.6 ± 0.6	$ \begin{array}{c} 10.3 \pm 1.0 \\ 8.0 \pm 0.9 \\ 2.3 \pm 0.2 \end{array} $	10.9 ± 1.0 8.5 ± 0.6 2.4 ± 0.6
Total Neutral Proteinase Macrophage	1.9 ± 0.6	1.4 ± 0.2	1.2 ± 0.1	1.2 ± 0.1
Elastase ^d Cathepsin G+ Neutrophil	0.9 ± 0.6	0.4 ± 0.1	0.3 ± 0.1	0.3 <u>+</u> 0.1
Elastase ^e	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.9 ± 0.1
Lavage Fluid:				
Total Acid Acoteinase Cathepsin D Cathepsin B	3.5 ± 0.6 2.1 ± 0.4 1.4 ± 0.5	$\begin{array}{c} 4.3 \pm 0.5 \\ 3.0 \pm 0.4 \\ 1.5 \pm 0.4 \end{array}$	4.0 ± 0.3 2.9 ± 0.8 1.1 ± 0.8	4.3 ± 0.5 2.7 ± 0.5 1.6 ± 0.4

 $^{^{}a}$ Mean \pm SE (N = 5-6). No differences were seen when the data were compared using the Student's t-test corrected for 3 comparisons. Also, no differences were noted in lung weights among the different exposure groups.

bnot inhibited by leupeptin cinhibited by leupeptin

dinhibited by 1,10 phenanthroline enot inhibited by 1,10 phenanthroline

Table 9

Lung and Lavage Fluid Proteinolytic Activity in Rats Exposed

to SY Dye for 90 Days and Allowed to Recover for 30 Days

mg protein released/hr/g lunga

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<u>Lung Tissue</u> :	<u>Control</u>	Low	<u>Medium</u>	<u>High</u>
Total Acid Proteinase Cathepsin D ^C Cathepsin B ^d	9.6 ± 0.5 8.1 ± 0.6 1.4 ± 0.5	10.5 ± 1.1 8.4 ± 0.7 2.1 ± 0.5	9.8 ± 0.7 7.8 ± 0.5 2.0 ± 0.4	9.4 ± 0.6 8.3 ± 0.5 1.1 ± 0.4
Total Neutral Proteinase Macrophage	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.1	0.3 ± 0.1
Elastase ^e Cathepsin G+ Neutrophil	0.1 ± 0.1	0.2 <u>+</u> 0.1	NDp	0.2 ± 0.1
Elastase	0.2 ± 0.1	0.1 ± 0.1	0.5 ± 0.2	0.1 ± 0.1
Lavage Fluid:				
Total Acid Proteinase Cathepsin D Cathepsin B	2.8 ± 0.2 1.0 ± 0.2 1.8 ± 0.3	2.8 ± 0.3 1.0 ± 0.2 1.9 ± 0.3	2.6 ± 0.1 1.3 ± 0.5 1.4 ± 0.6	2.2 ± 0.1 0.5 ± 0.1 1.6 ± 0.2

 $^{^{}a}$ Mean \pm SE (N = 5-6). No differences were seen when the data were compared using the Student's t-test corrected for 3 comparisons. Also, no differences were noted in lung weights among the different exposure groups.

 $^{^{}b}$ ND = none detected.

^cnot inhibited by leupeptin

dinhibited by leupeptin

einhibited by 1,10 phenanthroline

fnot inhibited by 1.10 phenanthroline

Lung Connective Tissue Biochemistry

Total lung collagen and airway fluid hydroxyproline content were measured in both control and SY dye exposed rats. Results showed no differences between control and exposed animals for these parameters after the 90-day exposure period (Table 10) or after the 30-day post-exposure recovery time (Table 11). Results were compared statistically using the Student's t-test corrected for 3 comparisons.

Hematology and Serum Clinical Chemistries

Hematology and serum clinical chemistry determinations were done on rats exposed to SY over a 90-day period and on serum from exposed rats that were allowed to recover for 30 days. The parameters measured in these determinations are listed on Table 12. No hematologic parameters were affected by exposure to yellow dye. However, marginal reductions in serum alkaline phosphatase and serum glutamic pyruvic transaminase (SGPT) activities in serum were seen after 90 days of exposure to the highest concentration of SY dye (Table 13). These changes returned to normal after the 30-day recovery period (Table 14). Total bilirubin and cholesterol concentrations in serum were increased after 90 days of exposure to the highest level of yellow dye. The serum enzyme changes, along with increased bilirubin and cholesterol, suggest minimal hepatic dysfunction which was no longer present 30 days post-exposure. No other exposure levels were affected, and this increase was no longer present after the 30-day recovery period. Thyroxine was not significantly affected by exposure to yellow dye (Tables 13 and 14).

Histopathology

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Ten males and ten females from each exposure group and time were sacrificed by intraperitoneal injections of T61 and examined for gross

Table 10

Lavage Fluid and Lung Tissue Collagen for Rats Exposed to SY Dye for 90 Days

	Lavage Fluid Collagen (\pug/g)*	Total Lung Collagen (mg/g)*
Control	31 <u>+</u> 4	18 <u>+</u> 1
Low	34 <u>+</u> 5	19 <u>+</u> 2
Medium	35 ± 5	16 ± 1
High	38 <u>+</u> 8	15 <u>+</u> 1

^{*}Normalized to grams of lung weight (mean \pm SE; n = 5-6). No differences were seen when the data were compared using Student's t-test corrected for 3 comparisons. Also, no differences were noted in lung weights among the different exposure groups.

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Table 11

Lavage Fluid and Lung Tissue Collagen for Rats Exposed
to SY Dye for 90 Days Followed by 30 Days of Recovery

	Lavage Fluid Collagen (ug/g)*	Total Lung Collagen (mg/g)*
Control	36 <u>+</u> 3	15 <u>+</u> 1
Low	30 ± 4	17 <u>+</u> 1
Medium	38 ± 4	16 <u>+</u> 1 , ,
High	35 <u>+</u> 5	15 <u>+</u> 1

^{*}Normalized to grams of control lung weight (mean \pm SE; n = 6). No differences were seen when the data were compared using the Student's t-test corrected for 3 comparisons. Also, no differences were noted in lung weights among the different exposure groups.

Table 12

Hematology and Serum Clinical Chemistry Measurements on Rats Exposed by Inhalation to SY or SY/SG Dye Aerosols for 90 Days

a. Hematology:

- 1) Hematocrit
- 2) Hemoglobin concentration
- 3) Erythrocyte count
- 4) Erythrocyte indices (mean cellular volume, mean cellular hemoglobin, mean cellular hemoglobin concentration)
- 5) Leukocyte count, total
- 6) Leukocyte count, differential

b. Serum Chemistry:

- 1) Total protein and albumin
- 2) Serum gamma-glutamyl transpeptidase*
- 3) Serum glutamic pyruvic transaminase
- 4) Serum alkaline phosphatase
- 5) Bilirubin (total)
- 6) Blood urea nitrogen
- 7) Creatinine
- 8) Calcium
- 9) Phosphorus
- 10) Sodium
- 11) Potassium
- 12) Chloride
- 13) Glucose
- 14) Cholesterol
- 15) Thyroxine (T_A)

^{*}No activity detected following the SY/SG exposures. Therefore, not measured after the SY exposures.

Table 13
Clinical Pathology Values of Rats
Exposed to SY Uye for 90 Days

 $(\bar{X} \pm SE, n = 11-12)$

<u>Biochemistry</u> :	Control	Low	<u> Medium</u>	High
Alkaline Phosphatase (IU/L)	72 <u>+</u> 6	67 <u>±</u> 7	63 <u>+</u> 5	57 <u>+</u> 4*
SGPT (IU/L)	40 <u>±</u> 7	36 <u>+</u> 5	33 <u>+</u> 2*	32 <u>+</u> 1*
Total bilirubin (mg/dL)	0.29 ± 0.03	0.30 ± 0.05	0.35 ± 0.04	0.38 <u>+</u> 0.03*
Thyroxine (µg/dL)	3.6 ± 0.3	3.7 <u>+</u> 0.4	3.7 ± 0.2	3.9 ± 0.5
Glucose (mg/dL)	230 <u>±</u> 40	190 <u>+</u> 20	190 <u>+</u> 20	180 <u>+</u> 20
Cholesterol (mg/dL)	72 <u>±</u> 13	78 <u>+</u> 16	85 <u>+</u> 18	113 <u>+</u> 13*
BUN (mg/dL)	21 <u>+</u> 2	18 <u>+</u> 2	19 <u>+</u> 2	18 <u>+</u> 2
Creatinine (mg/dL)	0.63 ± 0.02	0.58 ± 0.05	0.58 <u>+</u> 0.03	0.55 <u>+</u> 0.04
Inorganic Phosphorous (mg/dL)	6.0 <u>+</u> 0.8	5.7 <u>+</u> 0.5	6.2 <u>+</u> 0.7	6.0 <u>+</u> 0.6
Calcium (mg/dL)	11.0 <u>+</u> 1.4	11.1 <u>+</u> 1.2	10.4 ± 0.4	10.9 ± 0.7
Total Protein (g/dL)	6.3 <u>+</u> 0.4	6.3 <u>+</u> 0.4	6.3 <u>+</u> 0.2	6.5 <u>+</u> 0.3
Albumin (g/dL)	4.1 <u>+</u> 0.3	4.2 <u>+</u> 0.2	4.4 <u>+</u> 0.2	4.5 <u>+</u> 0.3

 $[*]P \le 0.05$ in Student-t statistic. Critical t-values were corrected for 3 comparisons.

Table 13 (continued)
Clinical Pathology Values of Rats
Exposed to SY Dye for 90 Days

 $(\bar{X} \pm SE, n = 11-12)$

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Fig. 674

<u>Biochemistry</u> :	Control	Low	<u>Medium</u>	<u>High</u>
Sodium (meq/L)	148 <u>+</u> 2	149 <u>+</u> 1	149 <u>+</u> 2	149 <u>+</u> 2
Potassium (meq/L)	6.0 <u>+</u> 1.0	5.6 ± 0.3	5.5 <u>+</u> 0.4	5.6 ± 0.4
Chloride (meq/L)	112 <u>+</u> 2	112 <u>+</u> 1	112 <u>+</u> 2	111 <u>+</u> 1
<u>Hematology</u> :				
RBC (10 ⁶ /mm ³)	7.1 ± 0.4	7.1 <u>+</u> 0.3	7.1 <u>+</u> 0.4	6.9 <u>+</u> 0.5
Hematocrit (%)	38 <u>+</u> 1	38 <u>+</u> 1	38 <u>+</u> 2	36 <u>+</u> 3
Hemoglobin (g/dL)	13.8 <u>+</u> 0.4	13.7 <u>+</u> 0.4	13.8 <u>+</u> 0.5	13.4 <u>+</u> 0.4
Mean Corpuscular Volume (µm³)	53 <u>+</u> 1	53 <u>+</u> 2	54 <u>+</u> 2	53 <u>+</u> 1
Mean Corpuscular Hemoglobin Concentration (%)	37 <u>+</u> 1	37 <u>+</u> 1	36 <u>+</u> 1	37 <u>+</u> 2
WBC (10 ³ /mm ³)	1.9 <u>+</u> 0.8	1.8 <u>+</u> 0.6	2.2 <u>+</u> 0.6	2.1 <u>+</u> 1.1
Neutrophils (10 ³ /mm ³)	0.6 ± 0.3	0.5 ± 0.2	0.6 ± 0.2	0.6 ± 0.2
Lymphocytes (10 ³ /mm ³)	1.3 <u>+</u> 0.5	1.2 ± 0.3	1.6 <u>+</u> 0.4	1.5 ± 0.9
Eosinophils (10 ³ /mm ³)	≤0.1	<u>≤</u> 0.1	≤0.1	≼٥.١
Basophils (10 ³ /mm ³)	<u><</u> 0.1	<u>≼</u> 0.1	<u>≼</u> 0.1	≤0.1

^{*}P \leq 0.05 in Student-t statistic. Critical t-values were corrected for 3 comparisons.

Table 13 (continued)

Clinical Pathology Values of Rats

Exposed to SY Dye for 90 Days

 $(\bar{X} \pm SE, n = 11-12)$

<u>Hematology</u> :	Control	Low	Medium	High
Monocytes (10 ³ /mm ³)	<u><</u> 0.1	<u><</u> 0.1	≤0.1	≤0.1
Banded Neutrophils (10 ³ /mm ³)	<u><</u> 0.1	<u>≤</u> 0.1	≤0.1	<u>≤</u> 0.1
NRBC (10 ³ /mm ³)	<u><</u> 0.1	<u><</u> 0.1	≤0.1	<u>≤</u> 0.1

 $[*]P \le 0.05$ in Student-t statistic. Critical t-values were corrected for 3 comparisons.

Table 14

Clinical Pathology Values of Rats Exposed to SY Dye
for 90 Days and Allowed to Recover for 30 Days*

 $(\hat{X} \pm SE, n = 11-12)$

<u>Biochemistry</u> :	Control	Low	Medium	High
Alkaline Phosphatase (IU/L)	72 <u>+</u> 8	73 <u>+</u> 9	70 <u>+</u> 4	75 ± 7
SGPT (IU/L)	44 <u>+</u> 5	49 <u>+</u> 11	38 <u>+</u> 4	,41 ± 7
Total bilirubin (mg/dL)	0.30 ± 0.11	0.33 ± 0.08	0.32 ± 0.12	0.40 ± 0.09
Thyroxine (µg/dL)	3.1 ± 0.4	3.4 ± 0.6	3.4 ± 0.6	3.9 ± 0.6
Glucose (mg/dL)	240 <u>+</u> 50	250 <u>+</u> 50	250 <u>+</u> 40	250 <u>+</u> 50
Cholesterol (mg/dL)	96 <u>+</u> 28	87 <u>+</u> 25	92 <u>+</u> 21	98 <u>+</u> 20
BUN (mg/dl)	24 <u>+</u> 1	24 <u>+</u> 1	24 <u>+</u> 1	25 <u>+</u> 3
Creatinine (mg/dL)	0.8 <u>+</u> 0.2	0.8 <u>+</u> 0.2	0.7 ± 0.2	0.7 <u>+</u> 0.1
Inorganic Phosphorous (mg/dL)	6.7 <u>+</u> 1.1	7.0 <u>+</u> 1.1	7.0 <u>+</u> 1.5	7.4 <u>+</u> 1.4
Calcium (mg/dL)	12.0 <u>+</u> 0.4	12.1 <u>+</u> 0.4	12.3 ± 0.7	12.0 <u>+</u> 0.8
Total Protein (g/dL)	7.9 <u>+</u> 0.2	8.1 ± 0.7	7.9 <u>+</u> 0.2	7.9 <u>+</u> 0.4
Albumin (g/dL)	5.0 ± 0.2	5.1 <u>+</u> 0.7	5.0 <u>+</u> 0.3	5.2 <u>+</u> 0.3

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^{*}There were no significant differences between treated and control groups at P < 0.05 in Student-t statistic. Critical t-values were corrected for 3 comparisons.

Table 14 (continued)

Clinical Pathology Values of Rats Exposed to SY Dye

for 90 Days and Allowed to Recover for 30 Days*

 $(\bar{X} \pm SE, n = 11-12)$

Biochemistry:	Control	Low	<u> Medium</u>	<u> High</u>
Sodium (meq/L)	147 <u>+</u> 2	148 <u>+</u> 3	148 <u>+</u> 4	144 <u>+</u> 9
Potassium (meq/L)	6.0 ± 0.7	5.7 ± 0.4	5.5 ± 0.4	5.6 ± 0.4
Chloride (meq/L)	110 <u>+</u> 2	111 <u>+</u> 2	110 ± 1	109 <u>+</u> 3
<u>Hematology</u> :				
RBC (10 ⁶ /mm ³)	7.4 ± 0.4	7.7 ± 0.4	7.7 <u>+</u> 0.4	7.7 ± 0.5
Hematocrit (%)	40 <u>+</u> 1	41 <u>+</u> 1	41 <u>+</u> 1	41 <u>+</u> 3
Hemoglobin (g/dL)	14.1 ± 0.3	14.4 <u>+</u> 0.4	14.5 ± 0.3	14.5 ± 0.3
Mean Corpuscular Volume (µm³)	53 <u>+</u> 2	53 ± 2	54 <u>+</u> 3	53 <u>+</u> 2
Mean Corpuscular Hemoglobin Concentration (%)	36 <u>+</u> 1	36 ± 1	35 <u>+</u> 1	36 <u>+</u> 1
WBC (10 ³ /mm ³)	2.4 ± 0.3	2.8 ± 0.1	3.1 ± 0.1	2.8 <u>+</u> 0.1
Neutrophils (10 ³ /mm ³)	0.7 ± 0.4	0.7 ± 0.3	0.8 ± 0.4	0.7 ± 0.4
Lymphocytes (10 ³ /mm ³)	1.7 <u>+</u> 0.6	2.0 ± 0.4	2.3 <u>+</u> 0.7	2.1 ± 0.7
Eosinophils (10 ³ /mm³)	<u><</u> 0.1	<u><</u> 0.1	<u><</u> 0.1	≤0.1

^{*}There were no significant differences between treated and control groups at P < 0.05 in Student-t statistic. Critical t-values were corrected for 3 comparisons.

Table 14 (continued)

Clinical Pathology Values of Rats Exposed to SY Dye
for 90 Days and Allowed to Recover for 30 Days*

 $(\bar{X} \pm SE, n = 11-12)$

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<u>Hematology</u> :	Control	Low	<u>Medium</u>	<u>High</u>
Basophils (10 ³ /mm ³)	≤0.1	<u><</u> 0.1	≤0.1	<u><</u> 0.1
Monocytes (10 ³ /mm ³)	<u><</u> 0.1	<u><</u> 0.1	≤0.1	<u><</u> 0.1
Banded Neutrophils (10 ³ /mm ³)	<u><</u> 0.1	<u>≤</u> 0.1	≤0.1	<u><</u> 0.1
NRBC (10 ³ /mm ³)	<u>≼</u> 0.1	<u>≤</u> 0.1	<u>≤</u> 0.1	<u><</u> 0.1

^{*}There were no significant differences between treated and control groups at P < 0.05 in Student-t statistic. Critical t-values were corrected for 3 comparisons.

lesions. Routine parafin embedded, 5 micron, hematoxylin and eosin stained slides from the following tissues were prepared for all animals: skin, tracheobronchial lymph node, popliteal lymph node, spleen, femur, larynx, nasal cavity (four levels), trachea, lung (four lobes), heart, stomach, duodenum, cecum, colon, liver, pancreas, kidneys, urinary bladder, epididymis, testis, prostate, uterus, ovary, adrenal, thyroid, brain, pituitary, eyes, and any gross lesions. Microscopic evaluation was performed on all of the listed tissues from the control and high dose groups. Tissues from the lower levels were evaluated to determine a no-effect level for each tissue having a treatment-related effect. Histopathologic evaluation of tissues from animals exposed to SY was done at Experimental Pathology Laboratories, Inc., Herndon, VA, by Dr. Deborah Banas, Diplomate ACVP. The following is a summary of the findings. The complete histopathology report for this 90-day SY exposure study can be found in Appendix I.

Ninety-Day Exposure

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Inhalation of SY dye at the high exposure concentration for 90 days resulted in submucosal pigment deposition in the nasal cavity of all rats. The pigment deposition was heaviest at medium and high levels. In the kidneys, an increase in granular pigment located in the cortical tubules was noted in all high dose rats. In the male rats, there was also an increase in the incidence of lesions characteristic of early chronic nephropathy, namely foci of regenerative tubular epithelium, casts, and foci of mononuclear cells. However, these lesions are commonly noted in rats of this age and strain and were only minimal to slight in severity. In the liver, minimal to slight granules of pigment were noted in the bile duct epithelium or hepatocytes adjacent to the bile duct in all high dose rats. In the lung,

minimal focal accumulations of foamy appearing alveolar macrophages containing a minimal amount of pigment were noted in the alveoli adjacent to the respiratory bronchioles in one male. This lesion was accompanied by minimal hyperplasia of Type II cells (granular pneumocytes).

In the rats exposed to SY at the medium exposure concentration, only nasal cavity, lung, liver, and kidneys were examined. In the nasal cavity, minimal submucosal pigment was noted at the medium level in three males and two females, and at the high concentration in five males and seven females. Pigment deposition in the kidneys was comparable to that of the controls. In the liver, minimal granules of pigment were noted in two females. No lesions attributable to treatment were noted in the sections of lung examined.

In the rats exposed to SY at the low exposure concentration, the nasal cavities of both sexes were examined. The livers of females were also examined. No compound-related histomorphologic alterations were noted in either of these tissues.

Thirty Day Recovery

Inhalation of SY dye at the high exposure concentration for 90 days, followed by a 30 day recovery period resulted in submucosal pigment deposition in the nasal cavities of all rats. This pigment deposition was heaviest at the medium and high levels, and was slightly less severe than was noted at the 90-day sacrifice. Increased pigment was noted in the kidney tubules and appeared to be less severe than that noted at the 90-day sacrifice. The incidence of early chronic nephropathy was comparable to that of the controls. In the liver, pigment deposition in the bile duct epithelium was comparable to that noted after the 90-day exposure. In the lungs, two males had minimal focal accumulations of foamy appearing alveolar macrophages

containing a minimal amount of pigment. These accumulations were accompanied by minimal hyperplasia of Type II cells (granular pneumocytes).

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In the rats exposed to SY dye at the medium exposure concentration for 90 days followed by a 30-day recovery period, only nasal cavity, lung, liver, and kidneys were examined. In the nasal cavity, minimal submucosal pigment was noted at the medium level in two males and four females and at the high level in six males and eight females. Slight submucosal pigment was noted at the high level in an additional male. Pigment deposition in the kidneys was comparable to the controls. No lesions attributable to treatment were noted in the lung or liver.

In the rats exposed to SY dye at the low exposure concentration, only the nasal cavity was examined. No compound-related histomorphological alterations were noted in these sections.

The finding of pigments in the nasal cavity, kidney and liver was examined in more detail at ITRI. Special stains (Prussian Blue for iron, periodic acid Schiff (PAS) and Hall's stain for bile) were made on sections of kidney, liver and lung to differentiate administered dye material in the tissues from autogenous pigments found in normal rats. The pigments in the control kidneys and some of the pigments in the exposed rats stained faintly with PAS indicating that they were probably a natural phenomenon that has been previously described. The major portion of the pigments in the exposed rats did not stain. It is hypothesized that the pigments in the nose, liver and kidney are metabolites of quinoline dye. Metabolism studies have shown that the dye is metabolized by the liver and excreted by the kidney. The pigment in the nasal cavity is present only under the olfactory epithelium, the epithelium where mixed function oxidases are concentrated. No pigments were

found in the tracheobronchial lymph nodes indicating that the dye was soluble enough to leave the lung before particle translocation to the lymph node took place.

Spontaneous disease lesions and incidental findings such as retinal degeneration, focal acinar atrophy of the pancreas, nematodiasis and nonsuppurative myocarditis occurred in a few rats in both control and treated groups at both sacrifice intervals. These lesions were distributed with approximately equal frequency in test and control rats, and thus were not exposure related (see Appendix I).

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90-DAY INHALATION EXPOSURE TO SY/SG DYE

Nominal exposure concentrations selected for this study were 0, 1, 10 and 100 mg/m³ given 6 hours/day, 5 days/week, for a period of 90 days. These exposure concentrations were selected on the basis of the same criteria as the 90 day SY dye exposure previously mentioned.

Statistical Analyses

Where possible, computer software packages such as BMDP, RS1 or Path/Tox were used for data handling and analysis. Standard tests applied to the experimental data were one-way analyses of variance, followed by tests for the equality of means, such as simple t-tests or multiple comparison t-tests² for the equality of medians. Usually a confidence level of 0.05 was used, although in some cases significance was expressed in much smaller or much larger values.

<u>Chemicals</u>

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SY/SG was supplied by the U. S. Army Medical Bioengineering Research and Development Laboratory (Fort Detrick, Frederick, MD). The purity of this dye material (QI and TA combined) was 95 percent and was used without further purification.

Animals and Animal Exposures

Male and female Fischer-344 (F344/Crl) rats, 15-20 weeks of age with an age range of ± 2 weeks, were used for this study. These animals were obtained from an existing colony raised at the Inhalation Toxicology Research Institute in which the disease surveillance monitoring of the colony was as previously described in this report. Rats were then acclimatized in exposure chambers, randomized into experimental groups, and cared for as described previously in this report for the 90 day inhalation exposure study of SY dye.

Animals were exposed to 3 levels of SY/SG dye material generated by a Jet-O-Mizer air jet mill as previously described. 3,4 The arrangement and entry groups of animals in the four Hazleton 2000 whole-body inhalation chambers used for this study (3 exposure and 1 air control), and chamber environment monitoring and maintenance were as previously described in this report for the 90 day inhalation study of SY dye. Concentration and size characteristics of the exposure atmospheres for each of the 63 exposure days are shown in Table 15. The SY/SG aerosol concentration was determined gravimetrically from filter samples taken daily from each exposure chamber. Aerosol size of the dye material was measured with a Lovelace Multi-Jet cascade impactor each day during the first week of exposure and at intervals as shown in Table 15 thereafter.

Clinical Observations

Detailed clinical observations were performed on all animals before exposures to ensure that they were in good health. Detailed clinical observations were also done at 6 weeks after the initiation of exposures, at the end of the 90 day exposures and after the 30 day recovery period. The animals were also observed twice daily for morbidity and mortality. No clinical abnormalities were noticed and all animals survived to sacrifice times.

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Animal Body Weights

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During this 3-month exposure, subsets of both male and female rats (n = 20 per sex) from each exposure chamber (including the control chamber) were weighed on a weekly basis. All animals were weighed after the last day of exposure. Those animals not sacrificed after the last day of exposure and held for the 30-day recovery were weighed at the end of this recovery period. Body weights measured throughout the study are summarized in Table 16. These

$\begin{array}{c ccccccccccccccccccccccccccccccccccc$			LOW		<u> MEDIUM</u>			HIGH			
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$		Conc.	MMA	Da	Conc.	MMA	10	Conc.	MM	AD	
Day 1 2.0 3.1 1.9 16.4 2.9 1.8 125 5.0 2.0 2 1.1 3.1 2.3 10.2 2.9 1.9 85 4.8 2.1 3 1.5 3.5 2.2 7.4 3.1 2.0 62 4.3 2.0 4 1.1 3.3 2.5 13.1 3.3 1.9 66 4.2 2.0 5 1.3 3.2 2.4 11.0 3.2 2.0 106 4.4 1.9 6 1.3 9.0 101 101 101 101 101 101 101 101 102 101 102 103		(mg/m^3)			(mg/m^3)	(µm)	وه	(mg/m ³)	(mm)	9	
3 1.5 3.5 2.2 7.4 3.1 2.0 62 4.3 2.0 4 1.1 3.3 2.5 13.1 3.3 1.9 66 4.2 2.0 5 1.3 3.2 2.4 11.0 3.2 2.0 106 4.4 1.9 6 1.3 9.0 101 101 101 101 101 101 101 101 101 101 102 102 102 102 103				1.9			1.8	125		2.0	
4 1.1 3.3 2.5 13.1 3.3 1.9 66 4.2 2.0 5 1.3 3.2 2.4 11.0 3.2 2.0 106 4.4 1.9 6 1.3 9.0 101 101 101 101 101 101 101 101 102 103 <td>2</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>	2										
5 1.3 3.2 2.4 11.0 3.2 2.0 106 4.4 1.9 6 1.3 9.0 101 101 101 101 101 101 101 101 101 102 103<											
6 1.3 9.0 101 7 0.7 2.0 1.9 12.5 113 8 1.3 14.1 3.3 2.0 86 4.1 1.9 9 0.8 6.0 72 10 1.1 12.0 107 11 1.7 9.8 97 12 1.9 10.0 61 3.9 2.8 13 1.7 9.9 3.0 1.8 78 14 0.8 2.5 2.4 9.8 95 15 0.9 10.8 123											
8 1.3 14.1 3.3 2.0 86 4.1 1.9 9 0.8 6.0 72 10 1.1 12.0 107 11 1.7 9.8 97 12 1.9 10.0 61 3.9 2.8 13 1.7 9.9 3.0 1.8 78 14 0.8 2.5 2.4 9.8 95 15 0.9 10.8 123	5		3.2	2.4		3.2	2.0		4.4	1.9	
8 1.3 14.1 3.3 2.0 86 4.1 1.9 9 0.8 6.0 72 10 1.1 12.0 107 11 1.7 9.8 97 12 1.9 10.0 61 3.9 2.8 13 1.7 9.9 3.0 1.8 78 14 0.8 2.5 2.4 9.8 95 15 0.9 10.8 123	9		2.0	1.0							
9 0.8 6.0 72 10 1.1 12.0 107 11 1.7 9.8 97 12 1.9 10.0 61 3.9 2.8 13 1.7 9.9 3.0 1.8 78 14 0.8 2.5 2.4 9.8 95 15 0.9 10.8 123	/		2.0	1.9		2 2	2.0				
10 1.1 12.0 107 11 1.7 9.8 97 12 1.9 10.0 61 3.9 2.8 13 1.7 9.9 3.0 1.8 78 14 0.8 2.5 2.4 9.8 95 15 0.9 10.8 123	8					3.3	2.0		4.1	1.9	
11 1.7 9.8 97 12 1.9 10.0 61 3.9 2.8 13 1.7 9.9 3.0 1.8 78 14 0.8 2.5 2.4 9.8 95 15 0.9 10.8 123	10										
12 1.9 10.0 61 3.9 2.8 13 1.7 9.9 3.0 1.8 78 14 0.8 2.5 2.4 9.8 95 15 0.9 10.8 123											
13 1.7 9.9 3.0 1.8 78 14 0.8 2.5 2.4 9.8 95 15 0.9 10.8 123					9.8				2 0	2.0	
14 0.8 2.5 2.4 9.8 95 15 0.9 10.8 123						2 0	1.0		3.9	2.8	
15 0.9 10.8 123			2.5	2.4		3.0	1.0				
			2.5	2.4							
10 0.4											
17 1.7 2.8 2.0 12.2 80			2.0	2 0							
			2.0	2.0		2 0	. o				
						2.0	1.9		2 6	1 0	
19 0.9 10.1 104 3.6 1.8 20 1.2 11.2 93									3.0	1.0	
21 0.5 2.4 2.0 11.3			2 1	2 0							
22 0.9 9.4 2.7 2.0 86			2.4	2.0		2.7	2.0				
23 0.6 9.4 2.7 2.0 26 4.0 1.9	23					2.7	2.0		4.0	1 0	
24 0.8 10.0 55									4.0	1.7	
25 1.2 13.2 B											
26 1.7 3.2 2.1 9.5 119	26		3 2	2 1							
27 1.0 9.6 3.1 2.1 132			3.2	2.,		3 1	2 1				
28 0.7 1.8 107 4.4 2.0						J.,			4 4	2.0	
29 0.7 5.3 113									7.7	2.0	
30 1.0 9.9 142	30										
31 1.0 2.7 2.1 14.0 123			2.7	2.1							
32 0.8 12.8 3.1 1.8 105			• • •	• • •		3.1	1.8				
33 1.0 13.3 98 4.2 1.9						0			4 2	1 9	
34 0.7 13.1 98									4.2		
35 0.6 9.6 131	35										
36 0.7 2.4 2.0 10.4 90	36		2.4	2.0	10.4						
37 0.9 12.5 3.0 1.9 9B						3.0	1.9				
38 0.7 10.2 101 3.8 1.8		0.7				5.0	1.3		3.8	1 8	
39 1.1 7.3 132									J. U		
40 1.0 9.4 117											

と、日本のであると、これの事を行っている。 関係のなっている 自動を行るのではなる 国際をおれたのなど 国力のないないが、国際などのない

Table 15 (Continued)

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		LOW		N	EDIUM				
	Conc.	MH	ADa	Conc.	MM	AD	Conc.	M	1AD
	(mg/m^3)	(µm)	a p	(mg/m^3)	(mm)	ق_	(mg/m^3)	(µm)	g
Day 41	0.3	2.4	2.1	2.2			108		
42	0.8			10.9	2.7	2.2	116		
43	1.0			7.1			69	4.2	1.9
44	0.4			3.6			135		
45	0.8			8.7			130		
46	0.8	2.6	1.9	13.5			131		
47	1.0			11.0	3.0	1.9	122		
48	0.9			11.6			109	3.8	1.8
49	0.6			13.4			90		
50	0.9			13.8			80		
51	1.1	2.5	1.9	12.7			93		
52	1.4			7.1	3.0	2.0	121		
53	1.4			11.1			111		
54	1.4			9.7			137		
55	3.5			11.5			102	3.9	1.8
56	0.8			13.4			103	• • • • • • • • • • • • • • • • • • • •	
57	3.6	2.9	2.1	11.5			120		
58	0.9			10.2	2.8	1.9	101		
59	0.8			15.1	• • •	***	126	4.1	1.7
60	0.9			12.8			113	***	
61	0.6	2.7	1.8	9.5			80		
62	1.1			3.4	2.7	1.9	100		
63	1.1			1.8	,		100	4.3	1.8
χ̄c	1.1	2.8	2.1	10.2	3.0	1.9	101	4.2	1.9
SD	±0.5	±0.4	<u>+</u> 0.2	<u>+</u> 3.1	<u>+</u> 0.2	<u>+</u> 0.1	±23	±0.4	+0.2

Daily chamber concentrations were determined by the mean of 3 two-hour samples taken during the day.

 $a_{\rm MMAD}$ = mass median aerodynamic diameter $b_{\sigma g}$ = geometric standard deviation chean values from day 1 through day 63

Table 16
Weekly Average Weights^a of Male and Female Rats for the 90-Day SY/SG Inhalation Exposure Study

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	-	rema le	158 ± 13	60	6 0	ر +	ا	1. J.	ار +	ا م	ا م	ار م	- -	+ م ب		وم + ا	+ 14
된	(10) mg/m³)		158	156	160 ±	166	168	170	173	176	177	179	181	178	180	178	186
High	(10)	49 le	251 ± 23	248 + 18	257 ± 18	265 ± 19	267 ± 19	274 ± 19	279 ± 18	287 ± 18	292 ± 19 ^b	299 ± 19	302 ± 19	299 ± 18	303 ± 17 ^D	301 ± 18 ^b	316 ± 26 ⁰
En:	(10.2 mg/m^3)	rema se	11 7 151	161 + 9	166 ± 991	169 ± 11	174 ± 9	177 ± 8	9 ∓ 081	181 + 11	191 + 9	187 ± 12	192 + 10	169 ± 9	194 ± 6	190 ± 8	191 ± 12
Med	(10.2 1	Male	260 ± 26	255 ± 19	271 + 18	282 ± 21	288 ± 20	294 ± 22	298 ± 25	284 ± 30	312 ± 23	316 ± 22	322 ± 23	319 ± 25	325 ± 23	322 ± 21	333 ± 55
MO	mg/m³)	rema le	156 ± 13	158 ± 6	9 7 191	171 ± 7	172 ± 6	173 ± 9	181 ± 7	183 + 8	7 + 061	189 ± 8	191 ± 7	187 ± 6	191 + 8	9 + 981	31 ± 061
Low	C.C.	M3.1e	253 ± 30	254 ± 15	21 + 172	289 ± 15	291 ± 15	291 ± 15	303 ± 15	307 ± 14	318 ± 13	319 + 14	322 ± 15	321 + 15	327 ± 14	325 ± 17	330 ± 25
Control			157 ± 11	166 ± 10	176 ± 9	174 ± 18	182 ± 13	180 ± 14	187 ± 13	11 7 11	198 ± 10	195 ± 15	6 + 661	192 ± 10	11 + 861	11 7 961	193 ± 11
Con	3	Male	258 ± 26	262 ± 30	263 ± 43	273 ± 40	273 ± 51	288 ± 34	299 + 36	300 + 29	319 ± 37	319 ± 36	321 ± 36	320 + 36	332 ± 40	327 ± 33	342 ± 23
			Week -3	0	2	က	4	2	9	_	80	6	10	=	12	13	11

^aAverage animal weight (grams) \pm S0, n = 20. ^bShown to be significantly lower than the control group of the same week interval using Dunnet's multiple comparisons procedure. P value \leq 0.01.

data show that rats exposed to the highest level of SY/SG dye gained weight at a significantly slower rate than controls, with female rats showing a difference in weight gain earlier than male rats. At the end of the 90-day exposures, high level exposed rats weighed approximately 7% less than control animals. However, after the 30-day post-exposure recovery period, there were no statistically significant differences in the weights of female rats among the four groups, while those of male rats exposed to the highest level of SY/SG dye remained significantly lower than male control animal weights.

Lung Content of QI and TA After Exposure to SY/SG Dye

At the end of the 3-month exposure, six rats (3 males and 3 females) from each chamber were sacrificed. Following each sacrifice, lungs were removed, homogenized in acetonitrile, the homogenate centrifuged, and the supernatant removed. The tissue pellet was then re-extracted with acetonitrile until no more dye was removed. The pooled acetonitrile extracts were analyzed for the major chemicals in the SY/SG dye mixture [2-(2'-quinoliny1)-1,3-indandione (Q1) and 1,4-di-p-toluidinoanthraquinone (TA)] by high pressure liquid chromatography. Conditions were:

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- reverse phase C_{1R} column, 25 cm x 4.6 mm.
- mobile phase; 9:1 acetonitrile:water to 100% acetonitrile gradient in 10 min, hold at 100% for 10 minutes
- flow rate, 1 mL/min
- detection: UV at 435 and 620 nm

Data in Table 17 indicate that virtually no QI remained in the lungs of rats sacrificed the day after the last day of exposure. However, in these same animals, approximately 19% of the calculated amount of TA that would have deposited in lungs during these exposures was found in lungs at every exposure level (Table 18).

Table 17
Lung Content of QI and TA After the 90-Day
Inhalation Exposure to SY/SG Dye Mixture

Aerosol Concentration	Lung Concentration (µg/g Lung ± SE)					
(mg/m ³)	10	TA				
<u>Male</u>						
Control	nd ^a	< 0.15				
1	nd	43 <u>+</u> 4				
10	nd	480 ± 20				
100	nd	3400 <u>+</u> 50				
<u>Female</u>						
Control	nd	< 0.18				
1	nd	39 <u>+</u> 2				
10	nd	370 ± 40				
100	nd	2800 <u>+</u> 200				

and=not detected at sensitivity of assay. Samples were assayed by high performance liquid chromatography with the sensitivity adjusted for the concentration of the TA. At these sensitivities, the assay would have detected as low as 0.1 ug QI/g lung in the low, 2.0 ug QI/g lung in the medium and 14 ug QI/g lung in the high level exposed lungs.

Table 18
Lung Burden of TA After a 90-Day
Exposure to SY/SG Dye Mixture

Aerosol Concentration	Lung Burdens Mean <u>+</u> SE (n = 3)	Calculated* Amount Deposited	Percent
(mq/m ⁻)	(mg/Lung)	<u>(mg/Lung)</u>	Retained
1	0.06 ± 0.003	0.32	·" 19 <u>+</u> 1
10	0.68 ± 0.03	3.2	21 <u>+</u> 1
100	5.70 ± 0.08	31.8	18 <u>+</u> 4
1	0.04 ± 0.001	0.24	17 ± 1
10	0.41 <u>+</u> 0.05	2.4	17 <u>+</u> 2
100	3.86 ± 0.34	23.8	16 <u>+</u> 3
	Concentration (mg/m ³) 1 10 100 1	Concentration Mean \pm SE (n = 3) (mg/m ³) (mg/Lung) 1 0.06 \pm 0.003 10 0.68 \pm 0.03 100 5.70 \pm 0.08 1 0.04 \pm 0.001 10 0.41 \pm 0.05	Aerosol Concentration (mg/m³)Lung Burdens Mean \pm SE (n = 3)Amount Deposited (mg/Lung)1 0.06 ± 0.003 0.32 10 0.68 ± 0.03 3.2 100 5.70 ± 0.08 31.8 1 0.04 ± 0.001 0.24 10 0.41 ± 0.05 2.4

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^{*}Assuming 63 6-hr exposures, 200 mL minute vol for males and 150 mL for females, 10% lung deposition, and 70 percent of SY/SG is TA.

In addition, 8 other groups of 6 rats (3 males and 3 females) were sacrificed 3, 7, 14, 30, 60, 90, 160 and 230 days after the last day of exposure and lungs were analyzed for SY/SG dye components. Again, virtually no QI was detected, but the quantity of TA found in lungs was significant at each of these post-exposure sacrifice times (Table 19 and Figure 1). This indicates that TA clears from lungs at a much slower rate than QI.

Respiratory Function

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Respiratory function data from measurements of rats before exposures, immediately after exposures and 30 days after exposures to SY/SG dye were analyzed by analysis of variance and comparison of the mean of each (low, medium and high) treated group to that of controls using the Student's t-test and the Bonferroni adjustment for multiple comparisons. A probability level of P < 0.05 was used as the criterion for statistical significance of all comparisons. The results are summarized in Tables 20-22. Not all variables measured are listed; data for body weight and the variables reflecting the major facets of respiratory function are presented. There were 16 rats per group before exposure and 14-16 at subsequent measurement times. The rats measured after exposure were the same as those measured before.

There were no significant differences between pre-exposure data from control or treated rats (Table 20). There were no physiologically meaningful differences between respiratory function of treated and control rats at the end of exposure (Table 21). As reported in Table 16, there was a dose-related trend toward lower body weights for treated rats than for controls, and the same trend was observed among the respiratory function groups. Since there were no significant differences among non-normalized function data between treated and control rats, there was a tendency for the weight-normalized

Table 19

Lung Retention of TA at Various Times After the 90-Day

Exposure to SY/SG Dye Mixture

Days After	Total Lung	Content of TA in mg ^a
Exposure	Male	<u>Female</u>
0	$5.7 \pm 0.1 (100)$	$3.9 \pm 0.3 (100)$
3	5.3 ± 0.6 (93)	$3.6 \pm 0.4 (92)$
7	5.8 ± 0.8 (102)	$3.9 \pm 0.2 (100)$
14	6.1 ± 0.5 (107)	3.6 ± 0.2 (92)
30	5.9 ± 0.2 (104)	$3.3 \pm 0.4 (85)$
60	$3.6 \pm 0.4 (63)$	3.4 ± 0.3 (87)
90	$3.3 \pm 0.5 (58)$	2.8 ± 0.4 (72)
160	$3.9 \pm 0.5 (69)$	2.6 ± 0.1 (66)
230	$3.6 \pm 0.5 (63)$	$2.1 \pm 0.1 (55)$

^aMeans \pm SE (n = 3). Numbers in parentheses are the percent of 0-day values.

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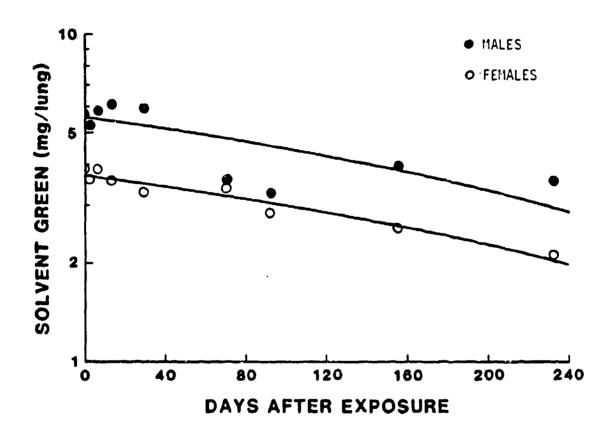


Table 20

Respiratory Function of Rats Before the SY/SG Dye Exposures*

Variable	Units	Control	± SE	100	38	Red tun	± SE	H1gh .	35
Body weight	₽	219	*	1\$6	12	196	=	190	2
Minute volume	mt/kg	385	2	430	=	=	15	919	16
Dynamic lung compitance	mil/cm H ₂ 0	63.0	0.05	92.0	0.05	0.31	0.05	0.28	0.01
Quasistatic chord compliance	mt/cm H ₂ 0	0.62	0.08	0.55	0.0 M	95.0	0.03	0.61	0.05
Total lung capacity (ILC)	, T	12.2	9.5	11.3	0.4	12.0	0.5	11.9	0.4
TLC/body weight	mt/kg	59.9	۶.۶	59.9	6.5	63.5	3.8	64.3	2.4
Vital capacity (VC)	ŧ	9.6	9.5	9.1	6 .4	9.5	•.0	9.1	0.4
AC/14C	ant /ant	0.80	0.0	0.80	0.05	0.80	0.05	0.81	0.01
Functional residual capacity (FRC)	¥	3.3	0.5	3.3	0.5	3.5	0.3	3.3	0.1
FRC/TLC		0.28	0.05	0.29	0.01	0.29	0.05	0.28	0.01
Residual volume (RV)	ť	5.4	0.5	2.2	0.2	2.4	₹.0	2.2	0.1
RV/TLC	16/16	C.20	0.0	0.20	0.05	0.30	0.05	0.19	0.01
CO diffusing capacity (PLCO)	mt/min/mm Hg	0.196	0.031	0.176	0.010	0.190	0.00	0.169	0.011
DLCO/alveolar volume	at/min/mm Hg/mt	0.018	0.00	0.011	0.001	0.018	0.00	0.017	0.00
Forced vital capacity (FVC)	ĭ	9.5	9.0	9.0	0.5	8.6	7.0	8 .6	0.5
Percent of FVC exhaled in 0.1 sec	percent	6	~	=	e	5	6	25	m
Mean midexpiratory flourate (MMES)	m/sec	=	•	35	•	#	1	5	٠
PRINE F / F V C	mt/sec/mt	7.	4.0	3.6	9.9	4 .8	9.0	4.8	0.5
Forced expiratory flowrate at					·				
10% of FVC (FEF10)	mt/sec	=	~	01	-	. 13	-	13	_
FEF10/FVC	mL/sec/mt	7.7	٥.٦	7.	0.1	1.3	0.2	- .	٥.٦
Slope of phase III of									
single breath N ₂ washout	percent N ₂ /mL	0.93	0.03	9.0	0.03	0.83	0.03	0.78	3 .

^{*}There were no significant differences between treated and control groups at P < 0.05.

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Table 21 Respiratory function of Rats at the End of 90-Day SV/56 Exposures*

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| 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 10

Variable	Units	Control	± SE	Low	SE	Redica	± SE	High	SE
Body weight	5	256	"	249	61	255	18	111	15
Minute volume	mt/kg	368	3	329	54	373	33	311	÷
Dynamic lung compliance	mt/cm H ₂ 0	0.32	0.05	0.32	0.03	0.32	0.0	0.35	0.05
Quasistatic chord compliance	BL/cm H ₂ 0	0.69	8.0	0.73	9. 8.	0.73	90.0	0.72	9 .0
Total lung capacity (TLC)		13.3	9.0	13.5	0.5	13.5	0.7	13.1	9.0
TLC/body weight	mL/kg	53.9	₽.2	57.1	3.4	54.4	1.9	62.1	۲.3
Vital capacity (VC)	ī	1.0	9.6	11.2	0.5	11.5	0.1	11.0	0.5
WC/TLC	mt/mt	0.83	0.01	0.83	0.01	0.85	0.01	0.84	0.01
Functional residual capacity (FRC)	ī	3.4	1.0	3.6	0.2	3.3	2.0	3.4	0.1
FRC/1LC	# /# 	92.0	0.01	0.27	0.0	0.25	0.0	0.26	0.01
Residual volume (RV)	¥	2.3	0.1	2.3	9.5	2.0	0.1	2.1	0.1
RV/1LC	mt /mt	0.18	0.0	0.17	0.01	0.15	0.0	9.16	0.01
CO diffusing capacity (DLCO)	mt/ssin/mm Hg	0.212	0.013	0.239	0.016	0.241	0.016	0.195	0.011
DLCG/alveolar volume	ml/min/mm Hg/ml	0.018	0.00	0.020	0.001	0.019	0.00	0.016	0.00
Forced vital capacity (FVC)	Ĕ	10.7	9.0	16.9	0.5	11.3	0.8	10.7	9.0
Percent of FVC exhaled in 0.1 sec	percent	41	6	25	7	20	က	25	~
Mean midexpiratory flowrate (MMEF)	mL/sec	45	9	8	2	\$	s	9	•
MARE / VC	mi/sec/ml	3.9	0.5	4.4	0.3	;	0.4	7.	9.4
Forced expiratory flowrate at									
10% of FVC (FEF10)	mL/sec	13	~	3 5	_	13	~	13	~
FEF10/FVC	mL/sec/mL	1.2	0.2	1.3	0.1	1.2	0.2	1.3	0.1
Slope of phase III of									
single-breath N ₂ washout	percent N ₂ /mL	0.83	90.0	0.79	0.01	0.75	0.08	0.73	8 .0

^{*}There were no significant differences between treated and control groups at P < 0.05.

Table 22

Respiratory Function of Rats 30 Days After the End of 90-Day SY-SG Dye Exposuras*

Variable	Units	Control	35 + 1	100	SE	Medium	± SE	High ± SE	SE
Body weight	5	292	39	255		259		223	91
Minute volume	mL/kg	295	12	305		322	-	336	92
Dynamic lung compliance	ML/cm H ₂ 0	0.37	0.03	0.39		0.35		0.39	0.05
Quasistatic chord compliance	ML/cm H ₂ O	0.11	9.0	0.11		0.11		0.74	0.03
Total lung capacity (TLC)	, ∉	14.1	9.0	14.1		14.1		13.5	9.0
TLC/body weight	mt/kg	56.3	2.3	58.0		6.95		62.4	2.7
Wital capacity (VC)	ť	11.7	9.9	11.9		11.9		11.5	9.9
VC/TLC	mt/mt	0.83	0.01	0.84		0.84		0.85	0.01
Functional residual capacity (FRC)	¥	3.5	٥.٦	3.7		3.6		3.4	0.1
FRC/ILC	mt/mt	0.25	0.0	0.27		0.25		0.25	0.01
Residual volume (RV)	¥	2.4	0.1	2.2		2.3		5.0	0.2
RW/TLC	mt./mt	0.17	0.0	91.0		9.16		0.15	0.01
CO diffusing capacity (DLCO)	mL/min/mm Hg	0.257	0.018	0.253		0.257		0.209	0.015
DLCO/alveolar volume	mL/min/mm Hg/mL	0.020	0.001	0.019		0.020		0.016*	0.001
Forced vital capacity (FVC)	¥	12.1	9.9	12.2		12.5		12.0	9.6
Percent of FVC exhaled in 0.1 sec	percent	55	~	75		2		99	€
Mean midexpiratory flowrate (MMEF)	mL/sec	9	S	23		62		3	•
MMEF/FVC	mL/sec/mL	5.0	♦.0	4.7		5.1		9.6	4.0
Forced expiratory flowrate at									
10% of FVC (FEF10)	mL/sec	36	~	96	~	, 19	~	18	_
FEF10/FVC	mL/sec/mL	7.	0.1	-	0.2	1.5	0.5	1.6	0.1
Slope of phase 111 of									
single-breath N ₂ washout	percent N ₂ /mL	0.11	0.0	0.63	0.01	0.65	0.08	0.65	0.01

*Significantly different from control at P < 0.05.

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values to be higher in treated rats. This trend only reached statistical significance for CO diffusing capacity/kg (not shown). There was little evidence of impairment of respiratory function at 30 days after the end of exposure (Table 22).

Only one statistically significant (P < 0.05) difference among the group means was detected by analysis of variance. The CO diffusing capacity normalized by alveolar volume was lower in the high level rats than in the other groups. The diffusing capacity itself was lower than that of controls, but only at the P < 0.10 level. There were no trends toward group differences in lung volume subdivisions. This means that there might have been a slight reduction in diffusing capacity (alveolar-capillary gas exchange) in the high level rats, but it was a combination of slight changes in opposite directions in two parameters that made the volume-normalized diffusing capacity significantly different. There were no other indications of function loss in exposed rats. Therefore, taken with the lack of function differences seen immediately after exposure, this result does not suggest that there was a physiologically significant effect of SY/SG dye exposure on respiratory function in this 90-day exposure study.

Lung Biochemistry

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Bronchoalveolar lavage fluid (BAL) was analyzed for indicators of injury after 6 and 13 weeks of exposure and after 30 days of recovery from the exposure. These results are summarized in Table 23. The data indicate an inflammatory response only in the lungs of rats exposed to the highest concentration (100 mg/m³). The inflammatory response was present after 6 weeks of exposure and, based on BAL analysis, did not appear to worsen by 13 weeks. Analysis of BAL from rats one month after the end of the exposure

Pulmonary Response of Rats Exposed to SY/SG for 90 Days

ås Observed in Bronchoalveolar Lavage Fluid

 $(\bar{X} \pm SE, n = 12)$

				w	Exposure Concentration (mg/m ³)	o)	ncentr	ation	Ē	(m ³)			1
	Sacrifice	Control	tro]		7-	Low		He	Medium 10	_	H1gh 101	6 ~	1
Lactate Dehydrogenase, mIU/g	13 13	490 390 370	+1+1+1	40 20 20	510 400 380	+1+1+1	30	520 450 380	1	20 30	1210 930 780	+1+1+1	50* 40*
Acid Phosphatase, mlU/g	6 51 71	9.7 9.2 7.9	+1+1+1	0.8 0.7 0.6	12.2 11.4 8.3	+1+1+1	1.8 0.7 0.8	11.0 10.9 1.7	+1+1+1	1.8 0.8 0.7	16.1	+1+1+1	2.2 1.0 0.6
ß-Glucuronidase, mIV/g	6 51	1.5 2.2 0.9	+1+1+1	0.2 0.8 0.1	1.9 7.1	+1+1+1	0.4	7.1	+1+1+1	0.2	7.2 5.7 3.4	+1+1+1	0.3* 0.8* 0.5*
Protein, mg/g	6 13	1.5 1.1 0.9	+1+1+1	0.2 0.2 0.1	e. r 0. r 4. r	+1+1+1	0.2	2.3	+1+1+1	0.3	3.2	+1+1+1	0.3* 0.6* 0.2*
Macrophages, 10 ³ cells/g	6 51 71	730 600 450	+1+1+1	0904	620 510 430	+1+1+1	50 60 40	860 460 580	+1+1+1	980 70	770 1000 580	+ + +	110 160* 70
Neutrophils, 10 ³ cells/g	6 13 71	5 0 7	+1+1+1	30%	30	+1+1+1	25 3	23 13 35	+1+1+1	35	1300 470 290	+1+1+1	130* 100* 50*

The values were normalized in this manner to take into account the difference in size of male versus avalues represent total amounts of material recovered in BAL divided by the net weight of the lung in g. There was no statistical difference in the mean net weight of the lungs between the group. female weights.

of the exposure (13 weeks). The 17 week sacrifice was of rats held for 1 month after the exposure Dan interim sacrifice was made after 6 weeks of exposure and a second sacrifice was made at the end

critical t-value necessary for rejection of the null hypothesis at P ≤ 0.05 was adjusted for *values differ from control values, $P \le 0.05$, by Bonferroni pairwise comparison of means. to determine if there was recovery from any exposure-related injury. Troumped the Street wester of the

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indicated that the inflammation was still present in the rats exposed to the high concentration of SY/SG (Table 23). This is not suprising, since the SG portion of the dye had not cleared from the lung at this time (Table 19).

Lung tissue and lavage fluid proteinolytic activities were also measured in control rats and rats exposed to SY/SG dye aerosols. Acid proteinase activity was higher at the highest dose level after 90 days exposure to green dye (Table 24). This change was still present after 30 days recovery (Table 25). The increased activity was related to cathepsin D and probably associated with modest inflammation. Neutral proteinase activity tended to be increased at the same times, however, these data are extremely variable and thus significance, if any, cannot be defined.

Lung Connective Tissue Biochemistry

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The collagen contents of bronchoalveolar fluid and of lung tissue were determined at the end of the 90-day exposure (Table 26) and after a 30-day recovery period (Table 27). Total lung collagen was not affected by exposure to SY/SG dye mixture. Lavage fluid collagen was increased after 90 days of exposure to the highest two levels of SY/SG dye mixture, suggesting that there was an increased turnover of the extracellular collagenous matrix. However, after 90 days of exposure and a 30-day recovery period, no differences were noted in rats exposed to the highest two levels of SY/SG dye mixture. The low level of green dye exposure did not affect rat lavage fluid collagen at any time.

Hematology and Serum Clinical Chemistries

Hematology and clinical chemistry measurements were made on 12 control rats and 12 rats at each concentration at the end of the 90-day exposure (Table 28) and after a 30 day recovery period (Table 29). Results showed slight changes in inorganic phosphorous which were not dose related. Parallel

Table 24 Lung and Lavage Fluid Proteinolytic Activity in Rats Exposed to SY/SG Dye for 90 Days

mg protein released/hr/g lunga

Lung Tissue:	Control	Low	Medium	High
Total Acid Proteinase Cathepsin D ^d Cathepsin B ^e	13.0 ± 1.0 8.1 ± 0.5 4.9 ± 0.7	13.0 ± 1.0 8.9 ± 0.7 4.1 ± 1.0	11.2 ± 0.6 7.8 ± 0.5 3.4 ± 0.5	$\begin{array}{c} 16.2 \pm 0.8^{b} \\ 10.7 \pm 0.4^{b} \\ 5.4 \pm 0.8 \end{array}$
Total Neutral Proteinase Macrophage	1.3 ± 0.1	1.7 ± 0.1	0.8 ± 0.1	1.5 <u>+</u> 0.1
Elastase ^f Cathepsin G & Neutrophil	0.4 ± 0.1	0.5 ± 0.1	0.1 ± 0.2	0.1 ± 0.1
Elastase9	0.9 ± 0.1	1.1 ± 0.1	0.8 ± 0.1	1.3 ± 0.1^{b}
Lavage Fluid:				
Total Acid Proteinase	1.2 ± 0.5	1.2 ± 0.4	1.2 ± 0.3	1.7 ± 0.3
Cathepsin D Cathepsin B	1.3 ± 0.5 ND ^c	$\begin{array}{c} 0.7 \pm 0.2 \\ 0.5 \pm 0.3 \end{array}$	$\begin{array}{c} 1.1 \pm 0.3 \\ 0.2 \pm 0.4 \end{array}$	$\begin{array}{c} 1.4 \pm 0.2 \\ 0.3 \pm 0.2 \end{array}$

 $[\]frac{\partial Hean + SE}{\partial Hean}$ No differences were noted in lung weights among the different exposure groups.

 $bP \le 0.05$ in Student-t statistic; corrected for 3 comparisons.

CND = none detected

dnot inhibited by leupeptin

einhibited by leupeptin finhibited by 1,10 phenanthroline

⁹not inhibited by 1,10 phenanthroline

Table 25

Lung and Lavage Fluid Proteinolytic Activity in Rats Exposed

to SY/SG Dye for 90 Days After the 30 Day Recovery Period

mg protein released/hr/g lunga

Lung Tissue:	Control	Low	Medium	High
Total Acid Proteinase Cathepsin D ^C Cathepsin B ^d	8.3 ± 0.7 6.7 ± 0.5 1.5 ± 0.6	$\begin{array}{c} 9.5 \pm 0.7 \\ 8.0 \pm 0.6 \\ 1.5 \pm 0.4 \end{array}$	$\begin{array}{c} 9.5 \pm 0.5 \\ 8.9 \pm 0.5^{b} \\ 0.6 \pm 0.2 \end{array}$	$\begin{array}{c} 12.1 \pm 0.8^{b} \\ 11.0 \pm 0.6^{b} \\ 1.1 \pm 0.4 \end{array}$
Total Neutral Proteinase Macrophage	0.6 ± 0.1	1.0 <u>+</u> 0.19	1.1 ± 0.19	1.2 ± 0.19
Elastase ^e	0.2 <u>+</u> 0.1	0.4 <u>+</u> 0.1	0.5 ± 0.1^{b}	0.4 ± 0.1
Cathepsin G & Neutrophil Elastase ^f	0.4 ± 0.1	0.7 ± 0.1	0.6 ± 0.1	0.9 ± 0.1b

Lavage Fluid: Total Acid Proteinase 3.4 + 0.8 1.7 + 0.3

iotal Acid Fioteillase	1.4 <u>+</u> 0.0	1.1 <u>+</u> U.3	1.4 2 0.4	1.0 ± 0.1
Cathepsin D	0.7 ± 0.1	1.1 ± 0.2	0.9 ± 0.3	1.4 ± 0.1
Cathepsin B	0.7 ± 1.0	0.6 ± 0.3	0.5 ± 0.4	0.4 ± 0.2

Mean \pm SE; (N = 8). No differences were noted in lung weights among the different exposure groups.

 $^{^{}b}P \leq 0.05$ in Student-t statistic; corrected for 3 comparisons.

Cnot inhibited by leupeptin

dinhibited by leupeptin

einhibited by 1,10 phenanthroline

fnot inhibited by 1,10 phenanthroline

gwithin the range of historical controls (0.2-2.5 mg protein released/hr/g lung)

Table 26
Lavage Fluid and Lung Tissue Collagen for Rats
Exposed to SY/SG Dye for 90 Days

 $(\bar{X} \pm SE, n = 6-8)$

	Lavage Fluid Collagen (µg/g)*	Total Lung Collagen (mg/g)*
Control	30 <u>+</u> 4	20 ± 2
Low	17 <u>+</u> 6	20 <u>+</u> 3
Medium	48 <u>+</u> 4**	16 <u>+</u> 3
High	57 <u>+</u> 6**	17 <u>+</u> 2

^{*}Normalized to grams of lung weight. No differences were noted in lung weights among the different exposure groups.

exposure groups. ** $P \le 0.05$ in Student-t test. Critical t-values were corrected for 3 comparisons.

Table 27

Lavage Fluid and Lung Tissue Collagen for Rats

Exposed to SY/SG Dye for 90 Days and Allowed to Recover for 30 Days

 $(\bar{X} \pm SE, n = 6-8)$

	Lavage Fluid Collagen (vg/g)*	Total Lung Collagen (mg/g)*
Control	33 <u>+</u> 5	16 <u>+</u> 1
Low	23 <u>+</u> 7	17 ± 2
Medium	31 <u>+</u> 5	17 <u>+</u> 2
High	43 + 5	16 <u>+</u> 2

^{*}Normalized to grams of lung weight. No differences were noted in lung weights among the different exposure groups.

Table 28 Clinical Pathology Values in Rats After 90 Day Exposure to SY/SG Dye

 $(\bar{X} \pm SE; n = 11-12)$

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Biochemistry:	Con	trol		<u>ow</u>		He	di	um	н	gh_	
Alkaline Phosphatase (IU/L)	88	<u>+</u> 5	78	±	2	77	<u>+</u>	3	61	±	2*
SGPT (IU/L)	54	<u>+</u> 8	54	±	9	44	±	3	40	±	4
Total Bilirubin (mg/dL)	0.22	± 0.02	0.24	±	0.02	0.23	<u>+</u>	0.02	0.30	±	0.04
Cholesterol (mg/dL)	71	± 7	58	±	5	83	±	11	123	<u>+</u>	23*
Thyroxine (µg/dL)	3.4	<u>+</u> 0.3	3.9	<u>+</u>	0.2	4.0	±	0.6	3.3	<u>+</u>	0.1
Glucose (mg/dL)	187	<u>+</u> 8	220	±	13*	260	±	21*	270	±	23*
BUN (mg/dL)	21	<u>+</u> 1	21	±	1	22	<u>+</u>	1	22	<u>+</u>	1
Creatinine (mg/dL)	0.58	<u>+</u> 0.02	0.61	±	0.02	0.61	<u>+</u>	0.02	0.63	1.	0.02
Inorganic Phosphorus (mg/dL)	5.0	<u>+</u> 0.3	5.5	±	0.2	6.5	±	0.6*	6.1	±	0.4*
Calcium (mg/dL)	10.4	<u>+</u> 0.1	10.9	±	0.1	11.0	<u>+</u>	0.1	11.9	±	0.3
Total Protein (g/dL)	6.3	<u>+</u> 0.1	6.8	±	0.1*	6.9	±	0.2*	7.2	±	0.2*
Albumin (g/dL)	4.0	± 0.1	4.5	<u>+</u>	0.1*	4.5	±	0.1*	4.8	±	0.1*
Gamma Glutamyl Franspeptidease (IU/L)			No Sig	n i f	icant	Activit	y I	Detecte	e d		

^{*}Value differs from control at P < 0.05 in Students' t-test. Critical t-values were corrected for 3 comparisons.

Table 28 (continued)
Clinical Pathology Values in Rats After 90 Day Exposure to SY/SG Dye

 $(\bar{X} + SE; n = 11-12)$

Hematology:	Control	Low	Medium	<u>High</u>
RBC (10 ⁶ /mm ³)	7.8 ± 0.1	7.7 ± 0.1	7.8 ± 0.2	7.7 ± 0.2
Hematocrit (%)	42 <u>+</u> 1	41 <u>+</u> 1	42 <u>+</u> 1	42 <u>+</u> 1
Hemoglobin (g/dL)	14.8 ± 0.1	14.8 ± 0.2	14.7 <u>+</u> 0.2	· 14.8 ± 0.1
Mean Corpuscular Volume (µm³)	54 <u>+</u> 1	54 <u>+</u> 1	54 <u>+</u> 1	54 <u>+</u> 1
Mean Corpuscular Hemoglobin Concentration (%)	35.0 ± 0.4	36.0 ± 0.3	35.0 ± 0.3	35.5 ± 0.3
WBC (10 ³ /mm ³)	6.2 <u>+</u> 0.5	5.4 ± 0.4	4.5 ± 0.6	4.8 ± 0.5
Neutrophils $(10^3/\text{mm}^3)$	1.1 ± 0.2	1.1 <u>+</u> 0.1	1.0 ± 0.1	1.4 ± 0.1
Lymphocytes (10 ³ /mm ³)	4.8 ± 0.3	4.3 ± 0.3	3.4 ± 0.5	3.3 ± 0.3
Eosinophils (10 ³ /mm ³)	<u>≤</u> 0.1	<u><</u> 0.1	≤0.1	<u>≤</u> 0.1
Basophils (10 ³ /mm ³)	≤0.1	<u><</u> 0.1	≤0.1	<u><</u> 0.1
Monocytes (10 ³ /mm ³)	<u><</u> 0.1	≤0.1	<u>≤</u> 0.1	<u>≼</u> 0.1
Banded Neutrophils (10 ³ /mm ³)	≤0.1	≤0.1	≤0.1	<u><</u> 0.1
NRBC (10 ³ /mm ³)	≤0.1	≤0.1	<u>≤</u> 0.1	≤0.1

^{*}Value differs from control at P < 0.05 in Students' t-test. Critical t-values were corrected for 3 comparisons.

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Table 29
Clinical Pathology Values in Rats After 90 Day Exposure
to SY/SG Dye and Allowed to Recover for 30 Days

 $(\bar{X} \pm SE; n = 12)$

Biochemistry:	Control			Low			Medium			High		
Alkaline Phosphatase (IU/L)	85	±	2	74	±	3	74	±	5	72	±	6
SGPT (IU/L)	42	±	2	47	±	5	39	<u>+</u>	3	39	<u>+</u>	2
Total Bilirubin (mg/dL)	C.28	±	0.01	0.32	<u>+</u>	0.02	0.30	<u>+</u>	0.03	0.26	±	0.02
Cholesterol (mg/dL)	74	±	6	71	<u>+</u>	7	70	<u>+</u>	7	75	±	7
Thyroxine (µg/dL)	1.77	±	0.11	1.77	±	0.15	1.70	±	0.17	2.71	±	0.19
Glucose (mg/dL)	220	<u>+</u>	10	220	±	10	210	±	20	230	±	10
BUN (mg/dL)	22	<u>+</u>	1	22	±	1	22	±	1	23	±	1
Creatinine (mg/dL)	0.54	±	0.02	0.59	±	0.02	0.58	±	0.01	0.58	±	0.02
Inorganic Phosphorus (mg/dL)	5.3	±	0.3	5.1	<u>+</u>	0.3	5.2	±	0.3	5.9	±	0.3
Calcium (mg/dL)	12.1	<u>+</u>	0.3	11.8	±	0.2	11.8	±	0.4	12.4	<u>+</u>	0.2
Total Protein (g/dL)	6.6	±	0.1	6.5	±	0.1	6.7	±	0.2	6.9	±	0.1
Albumin (g/dL)	4.3	<u>+</u>	0.1	4.4	±	0.1	4.4	<u>+</u>	0.1	4.5	<u>+</u>	0.1
Gamma Glutamyl Transpeptidease (IU/L)				No Sig	nif	icant	Activit	у (etect	ed		

Table 29 (continued)

Clirical Pathology Values in Rats After 90 Day Exposure
to SY/SG Dye and Allowed to Recover for 30 Days*

 $(\bar{X} \pm SE; n = 12)$

Hematology.	Control	Low	Medium	High
RBC (10 ⁶ /mm ³)	8.1 ± 0.2	8.0 ± 0.2	8.3 ± 0.1	8.3 <u>+</u> 0.3
Hematocrit (%)	44 <u>+</u> 1	43 <u>+</u> 1	44 <u>+</u> 1	44 <u>+</u> 1
Hemoglobin (g/dL)	15.0 <u>+</u> 0.1	15.2 ± 0.1	15.3 ± 0.2	15.5 ± 0.2
Mean Corpuscular Volume (µm³)	54 <u>+</u> 1	54 <u>+</u> 1	53 <u>+</u> 1	53 <u>+</u> 1
Mean Corpuscular Hemoglobin Concentration (%)	34.6 ± 0.3	35.4 ± 0.2	34.7 ± 0.2	35.8 ± 1.0
WBC (10 ³ /mm ³)	5.4 ± 0.6	4.9 ± 0.4	3.7 ± 0.3	4.6 ± 0.5
Neutrophils $(10^3/\text{mm}^3)$	1.6 ± 0.7	0.9 ± 0.1	1.0 ± 0.2	1.3 ± 0.3
Lymphocytes (10 ³ /mm³)	4.1 ± 0.3	3.9 ± 0.3	2.6 ± 0.2	3.3 ± 0.2
Eosinophils (10 ³ /mm ³)	<u><</u> 0.1	<u>≤</u> 0.1	<u><</u> 0.1	<u>≼</u> 0.1
Basophils (10 ³ /mm ³)	<u><</u> 0.1	<u><</u> 0.1	<u><</u> 0.1	<u><</u> 0.1
Monocytes (10 ³ /mm ³)	<u><</u> 0.1	<u><</u> 0.1	≤0.1	<u><</u> 0.1
Banded Neutrophils $(10^3/\text{mm}^3)$	<u><</u> 0.1	<u><</u> 0.1	≤0.1	<u>≤</u> 0.1
NRBC (10 ³ /mm ³)	<u><</u> 0.1	≤0.1	<u>≤</u> 0.1	<u><</u> 0.1

^{*}There were no significant differences between treated and control groups at $P \leq 0.05$.

and slight changes in albumin and total protein appeared to be dose related. Cholesterol was increased only at the highest dose. Glucose showed the largest change of the parameters examined and this was a dose related increase. The cause of these changes is unknown, but appears to have little clinical significance in light of the normal BUN, creatinine and SGPT levels indicating normal kidney and liver function. Serum electrolytes (sodium, potassium and chloride) were not analyzed because an insufficient volume of serum was obtained.

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No significant differences were seen in any of the measured clinical chemistry endpoints between each group of dye exposed rats and control animals 30 days after the last day of exposure. Thus, the serum biochemistry changes that were observed immediately following the 90-day exposures to SY/SG dye (Table 28) were apparently reversible during this 30-day post-exposure recovery period (Table 29).

<u>Histopathology</u>

Ten males and ten females from each exposure and time were sacrificed by intraperitoneal injections with T61 and examined for gross lesions. Routine parafin embedded, 5 micron, hematoxylin and eosin stained slides from the following tissues were prepared for all animals: skin, tracheobronchial lymph node, popliteal lymph node, spleen, femur, larynx, nasal cavity (four levels), trachea, lung (four lobes), heart, stomach, duodenum, cecum, colon, liver, pancreas, kidneys, urinary bladder, epididymis, testis, prostate, uterus, ovary, adrenal, thyroid, brain, pituitary, eyes, and any gross lesions.

Microscopic evaluation was performed on all of the listed tissues from the control and high dose groups. Tissues from the lower levels were evaluated to determine a no-effect level for each tissue having a treatment-related

effect. Histopathologic evaluation of tissues from animals exposed to SY/SG was done at Experimental Pathology Laboratories, Inc., Herndon, VA, by Dr. Deborah Banas, Diplomate ACVP. The following is a summary of the findings. The complete histopathology report for this 90-day SY/SG exposure study can be found in Appendix II.

Ninety-Day Exposure

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Inhalation of SY/SG dye mixture at 100 mg/m³ six hours/day, five days/week for 13 weeks resulted in changes in the lungs, nasal cavity, tracheobronchial lymph nodes, kidneys, and liver. In the lungs, slight to moderate accumulations of foamy appearing alveolar macrophages containing minimal to slight amounts of pigment were noted in the alveoli adjacent to the respiratory bronchioles in all high dose rats. These accumulations of alveolar macrophages were accompanied by slight to moderate hyperplasia of Type II cells (granular pneumocytes). In the nasal cavity, submucosal piyment deposition was noted at most levels of the nasal cavities of nearly all high dose rats. The pigment deposition was heaviest at Level III and Level IV. (Level I is the most anterior portion of the nasal cavity and Level IV is the most posterior. Level IV is mainly olfactory tissue.) In the tracheobronchial lymph node, hyperplasia of foamy macrophages (reticuloendothelial cells) with minimal pigment deposition and slight to moderately severe lymphoid hyperplasia were present. In the kidneys, an increase in granular pigment present in the cortical tubules was noted in all high dose rats. In the liver, minimal granules of pigment were noted in the bile duct epithelilum or hepatocytes adjacent to the bile ducts in all high dose rats.

In the rats exposed to SY/SG mixture at 10 mg/m³, only lung, nasal cavity, tracheobronchial lymph node, liver, and kidneys were examined. Minimal lung lesions similar to those noted in the high dose rats occurred in three males and three females. The lesions were single lesions and tended to be at the margins of the lung lobes. In the nasal cavity, minimal submucosal pigment was noted at Level III in one male and four females, and at Level IV in two females. In tracheobronchial lymph nodes, hyperplasia of foamy macrophages with minimal pigment deposition was noted in two males and two females. Lymphoid hyperplasia was noted in an additional male. Pigment deposition in the kidneys was comparable to the controls. In the liver, minimal granules of pigment were noted in two females.

In the rats exposed to SY/SG dye mixture at 1 mg/m³, the lungs and nasal cavities from both sexes were examined. The livers from females were also examined. No compound-related histomorphologic alterations were noted in any of these tissues.

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The pigments in the tissues of the exposed rats are similar to the pigments seen after exposure to SY dye alone.

Thirty-Day Recovery

Inhalation of SY/SG dye mixture at 100 mg/m³ for 90 days followed by a 30-day recovery period resulted in lung lesions similar to those noted after 90 days, but marginally less severe. Additionally, in the lungs, a few of the foamy macrophages containing pigment were present in the peribronchial lymphoid cuffs, a feature not present after 90 days exposure. In the nasal cavity, submucosal pigment deposition was present at most levels in nearly all high dose rats, but appeared to be slightly less severe than was noted after 90 days. In the tracheobronchial lymph nodes, hyperplasia of foam?

macrcphages containing a minimal amount of pigment was slightly more severe than was noted after 90 days exposure. The extent of lymphoid hyperplasia was similar to that at the end of exposure. In the kidney tubules, the increased tubular pigment was less severe than was noted after 90 days. In the liver, pigment deposition in the bile duct epithelium was comparable to that noted after 90 days exposure.

In the rats exposed to SY/SG dye mixture at 10 mg/m³ for 90 days followed by a 30-day recovery period, only lung, nasal cavity, trachecoronchial lymph node, liver and kidneys were examined. Lesions similar to those noted at this level after 90 days exposure were present. Minimal lung lesions were noted in two rats of each sex and submucosal pigment deposition was noted in the nasal cavity of single rats of each sex at Level II, six males and five females at Level III, and two males and six females at Level IV. Lymphoid hyperplasia was present in the tracheobronchial lymph node of one male, but hyperplasia of foamy macrophages was not present in any of the lymph nodes examined. Pigment was noted in the kidneys and was comparable to that of the controls. Thus, this does not appear to be exposure related. No pigment deposition was noted in the liver.

No compound-related histomorphologic alterations were noted in the lungs and nasal cavities of rats exposed to 1 mg/m^3 for 90 days followed by a 30-day recovery period.

Spontaneous disease lesions and incidental findings such as nonsuppurative myocarditis, testicular atrophy, prostatitis, and nematodiasis occurred in a few rats in both control and treated groups at both sacrifice intervals. These lesions were distributed with approximately equal frequency in test and control rats, and thus were not exposure related (see Appendix II).

SUMMARY OF THE 90-DAY REPEATED INHALATION EXPOSURE OF RATS TO DYE AEROSOLS

Male and female F344 rats were exposed by inhalation to 1.0 \pm 0.2, 10.8 ± 1.8 or 100 ± 17 mg/m³ (mean \pm SD) of SY dye aerusol for 6 hr/day, 5 days/wk for a period of 90 days. The average particle size of these aerosols ranged from 2.1 to 4.0 µm (mass median aerodynamic diameter). Following exposures, lung concentrations of QI were measured, which indicated that very little SY dye was retained in lungs and thus the amount deposited had cleared at a very rapid rate. Exposed animals were also evaluated for changes in respiratory function, biochemical indications of lung tissue damage, changes in blood chemistries, and histopathological lesions. At the end of the exposure, both male and female rats exposed to the highest concentration of SY dye had slightly, but statistically significant lower body weights than control animals. These lower body weights of male rats exposed to the highest concentration of SY returned to control values during the 30-day recovery period, while those of female rats did not. Exposure-related histopathological lesions in rats exposed to the highest concentration of SY dve (100 mg/m³) consisted of pigment deposition in the nasal cavity, liver, and kidney. In the lungs, accumulation of foamy alveolar macrophages containing minimal pigment was noted in one male. After a four-week recovery period, the amount of pigment deposited was slightly decreased. Minimal lung lesions were noted in two rats. Exposure of rats to 10 $\mathrm{mg/m}^3$ of SY dye did not result in lesions. Only pigment deposition in the nasal cavity was noted and to a much lesser degree than was noted at the high dose exposure. After a four-week recovery period, the pigment deposition in the nasal cavity was

still present. No compound-related histomorphological changes were seen in the tissues examined from rats exposed to 1 mg/m^3 of SY dye. No other toxicologically significant effects were observed in exposed animals as compared to control rats. Therefore, the no-observable-adverse effects level for SY dye inhalation exposures was 10 mg/m^3 for this particular exposure regime.

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Male and female F344 rats were also exposed by inhalation to 1.1 ± 0.5. 10.2 ± 3.1 or $101 \pm 23 \text{ mg/m}^3$ (mean $\pm SD$) of SY/SG dve aerosol for 6 hr/day. 5 days/wk for a period of 90 days. The average particle size of these aerosols ranged from 2.8 to 4.2 µm (mass median aerodynamic diameter). After exposures, the SY portion of this dye mixture (QI) cleared from lungs at a rapid rate, but substantial amounts of the SG portion of this dye mixture (TA) remained in lungs for an extended period after the exposure. As in the 90-day exposure study to SY dye, rats exposed to the highest concentration of SY/SG dye mixture gained weight at a slower rate than the other experimental groups of animals. However, after the 30-day post-exposure period, only females returned to control body weight values. Analysis of bronchoalveolar lavage fluid indicated an inflammatory response only in the lungs of rats exposed to the highest concentration of SY/SG dye (100 mg/m 3). which was present after 6 weeks of exposure, did not worsen after 13 weeks of exposure, and was still present after the 30-day recovery period. Increased acid proteinase in the highest two exposure levels at the end of exposure suggested an inflammatory response. However, after 30-day post-exposure period, only the highest exposure level was still increased, suggesting a gradual reduction in severity over time. Exposure-related histopathological lesions in rats exposed to the highest concentration of SY/SG dye (100

mg/m³) consisted of accumulations of foamy alveolar macrophages containing minimal amounts of pigment in the lungs. These accumulations were accompanied by hyperplasia of Type II pneumocytes. Similarly, foamy macrophages with pigment had accumulated in the tracheobronchial lymph nodes. Pigment deposition was noted in the nasal cavity, liver, and kidney. After a 30-day recovery period, these lesion; were decreased in severity with the exception of foamy macrophages in the tracheobronchial lymph nodes which were slightly increased. Exposure of rats to 10 mg/m³ of SY/SG dye resulted in minimal lesions in the lungs and tracheobronchial lymph nodes of a few rats and pigment deposition in the nasal cavity to a much lesser degree than was noted at the high dose exposure. After a 30-day recovery period, these minimal lesions were essentially unchanged. No compound-related histomorphological changes were seen in the tissues examined from animals exposed to 1 mg/m³ of SY/SG dye mixture. Therefore, the no-observable-adverse effects level for SY/SG dye inhalation exposures was 1 mg/m³.

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LITERATURE CITED

- Henderson, R. F., D. E. Bice, Y. S. Cheng, J. S. Dutcher, F. F. Hahn, T. C. Marshall, J. L. Mauderly, J. A. Pickrell, F. A. Seiler, J. D. Sun, and J. E. White. September 10, 1984. Studies on the Inhalation Toxicity of Dyes Present in Colored Smoke Munitions. Final Report for Phase III Studies: Four-Week Inhalation Exposures of Rats to Dye Aerosols, AD A156698. Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute, Albuquerque, NM.
- Games, P. A. 1977. An Improved t Table for Simultaneous Control on g Contrasts. J. Amer. Stat. Assoc. 72: 531-534.
- 3. Henderson, R. F., Y. S. Cheng, J. S. Dutcher, T. C. Marshall, and J. E. White. 1984. Studies on the Inhalation Toxicity of Dyes Present in Colored Smoke Munitions. Final Report for Phase I Studies: Generation and Characterization of Dye Aerosol, AD A142491. Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute, Albuquerque, NM.
- 4. Cheng, Y. S., T. C. Marshall, R. F. Henderson, and G. J. Newton. 1985.
 Use of a Jet Mill for Dispensing Dry Powder for Inhalation Studies. <u>Am.</u>
 <u>Ind. Hyg. Assoc. J.</u> 46: 449-454.
- 5. Schum, M. and H. C. Yeh. 1980. Theoretical Evaluation of Aerosol
 Depostion in Anatomical Models of Mammalian Lung Airway. <u>Bull. Math.</u>
 <u>Biol.</u> 42: 1-15.

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LITERATURE CITED (Continued)

- 6. Harkema, J. R., J. L. Mauderly, and F. F. Hahn. 1982. The Effects of Emphysema on Oxygen Toxicity in Rats. <u>Am. Rev. Respir. Dis.</u> 126: 1058-1065.
- 7. Henderson, R. F. 1984. Use of Bronchoalveolar Lavage to Detect Lung

 Damage. Environ. Health Perspect. 56: 115-129.

GLOSSARY

Green component of yellow/green dye: green dye, solvent green, SG

Major compound in yellow dye: 2-(2'-quinolinyl)-1,3-indandione, QI

Major compound in green dye: 1.4-di-p-toluidinoanthraquinone, TA

Stock yellow dye: yellow dye folvent yellow, SY

Stock yellow/green dye: yellow/green dye mix, SY/SG

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14

APPENDIX I

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

LOVELACE PROJECT NUMBER RZ-79

13 WEEK AND 17 WEEK INHALATION STUDY ON SOLVENT YELLOW DYE

PATHOLOGY REPORT

Submitted to:

Lovelace Biomedical and Environmental Research Institute, Inc. Albuquerque, New Mexico 87185

February 17, 1986

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

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PATHOLOGY SUMMARY

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EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

LOVELACE PROJECT NUMBER RZ-79

13 WEEK AND 17 WEEK INHALATION STUDY ON SOLVENT YELLOW DYE

PATHOLOGY SUMMARY

A histopathologic evaluation of selected tissues from male and female rats exposed to Solvent Yellow Dye was conducted to provide information on the inhalation toxicity of dyes present in colored smoke munitions. The experimental design for this study was as follows:

		Number of Animals					
Group	Concentration	13-Week Males	Sacrifice Females		Sacrifice Females		
С	Control	10	10	10	10		
L	Low Exposure Concentration	10	10	10	10		
M	Medium Exposure						
	Concentration	10	10	10	10		
Н	High Exposure Concentration	10	10	10	10		

According to protocol, routine hematoxylin and eosin stained slides from the following tissues were prepared for all animals: skin, tracheobronchial lymph node, popliteal lymph node, spleen, femur, larynx, nasal cavity (four levels), trachea, lung (four lobes), heart, stomach, duodenum, cecum, colon, liver, pancreas, kidneys, urinary bladder, epididymis, testis, prostate, uterus, ovary, adrenal, thyroid, brain, pituitary, eyes, and any gross lesions. Microscopic evaluation was performed on all of the listed tissues from the control and high dose groups. Tissues from the lower levels were evaluated to determine a no-effect level for each tissue having a treatment-related effect.

In general, the tissues called for to be examined by protocol are represented in the Histopathology Incidence Tables. Only a few tissues were inadvertently missed at the time of necropsy or lost during istologic processing. In some instances, the posterior portion of the nasal cavity had been damaged and complete sections of four levels of the nasal cavity could not be obtained.

Microscopic findings for each tissue examined from each animal are listed in the Histopathology Incidence Tables. All lesions are summarized by treatment groups in the Summary Incidence Tables together with the total number of animals in each group for which the tissues were examined. A tabulation of gross lesions observed at the time of necropsy with the corresponding microscopic change, if appropriate, is given in the Correlation of Gross and Microscopic Findings Tables. The descriptions of gross findings on these tables were transcribed from the Individual Animal Necropsy Sheets prepared at the time the necropsies were performed.

RESULTS

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13-Week Sacrifice

Inhalation of Solvent Yellow Dye at the high exposure concentration for 13 weeks resulted in submucosal pigment deposition in the nasal cavity of all rats. The pigment deposition was heaviest at Level III and Level IV. In the kidneys, an increase in granular pigment located in the cortical tubules was noted in all high dose rats. In the male rats, there was also an increase in the incidence of lesions

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characteristic of early chronic nephropathy, namely foci of regenerative tubular epithelium, casts, and foci of mononuclear cells. However, these lesions are commonly noted in rats of this age and strain and were only minimal to slight in severity. In the liver, minimal to slight granules of pigment were noted in the bile duct epithelium or hepatocytes adjacent to the bile duct in all high dose rats. In the lung, minimal focal accumulations of foamy appearing alveolar macrophages containing a minimal amount of pigment were noted in the alveoli adjacent to the respiratory bronchioles in one male. This lesion was accompanied by minimal hyperplasia of Type II cells (granular pneumocytes).

In the rats exposed to Solvent Yellow Dye at the medium exposure concentration, only nasal cavity, lung, liver, and kidneys were examined. In the nasal cavity, minimal submucosal pigment was noted at Level III in three males and two females, and at Level IV in five males and seven females. Pigment deposition in the kidneys was comparable to the controls. In the liver, minimal granules of pigment were noted in two females. No lesions attributable to treatment were noted in the sections of lung examined.

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In the rats exposed to Solvent Yellow Dye at the low exposure concentration, the nasal cavity was examined from both sexes; the liver was also examined from the females. No compound-related histomorphologic alterations were noted in either of these tissues.

17-Week Sacrifice

Inhalation of Solvent Yellow Dye at the high exposure concentration for 13 weeks followed by a four-week recovery period resulted

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in submucosal pigment deposition in the nasal cavity of all rats. This pigment deposition was heaviest at Level III and Level IV and was slightly less severe than was noted at the 13-week sacrifice. In the kidney tubules, increased tubular pigment was noted and appeared to be less severe than that noted at the 13-week sacrifice. The incidence of early chronic nephropathy was comparable to that of the controls. In the liver, pigment deposition in the bile duct epithelium was comparable to that noted after 13 weeks exposure. In the lungs, two males had minimal focal accumulations of foamy appearing alveolar macrophages containing a minimal amount of pigment. These accumulations were accompanied by minimal hyperplasia of Type II cells (granular pneumocytes).

In the rats exposed to Solvent Yellow Dye at the medium exposure concentration for 13 weeks followed by a four week recovery period, only nasal cavity, lung, liver, and kidneys were examined. In the nasal cavity, minimal submucosal pigment was noted at Level III in two males and four females and at Level IV in six males and eight females. Slight submucosal pigment was noted at Level IV in an additional male. Pigment deposition in the kidneys was comparable to the controls. No lesions attributable to treatment were noted in the lung or liver.

In the rats exposed to Solvent Yellow Dye at the low exposure concentration, only the nasal cavity was examined. No compound-related histomorphological alterations were noted in these sections.

Spontaneous disease lesions and incidental findings occurred in rats in both control and treated groups at both sacrifice intervals.

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- These lesions were distributed with approximately equal frequency in test and control rats.

CONCLUSIONS

Exposure of rats to Solvent Yellow Dye at the high exposure concentration for 13 weeks resulted in pigment deposition in the masal cavity, liver, and kidney. In the lungs, accumulation of foamy alveolar macrophages containing minimal pigment was noted in one male. After a four-week recovery period, the pigment deposition was slightly decreased in severity. Minimal lung lesions were noted in two rats.

Exposure of Solvent Yellow Dye at the medium exposure concentration for 13 weeks resulted in pigment deposition in the nasal cavity to a much lesser degree than was noted at the high dose exposure. After a four-week recovery period, the pigment deposition in the nasal cavity was still present.

Exposure of rats to Solvent Yellow Dye at the low exposure concentration did not result in any compound-related histomorphologic changes in the tissues examined.

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Veterinary Pathologist

February 17, 1986

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EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

QUALITY ASSURANCE REPORT CERTIFICATION

	lace Biomedical and Enviror ntal Research Institute, In		No. RZ-79
Study Director _	Dr. Larry A. Ackerman Path	nologist <u>Dr. D</u>	eborah A. Banas
Study Title 13 W	eek and 17 Week Inhalation	Study on Solvent	Yellow Dye
Test Article	Solvent Yellow Dye	Species	Rats
All parts of	the pathology phase of this	s study, includin	g the final report,
were reviewed	by Experimental Pathology	Laboratories Qua	lity Assurance Unit
on April 23	, 1985 through August 27, 1	1985 . All find	ings were reported
to the Study	Director and Management.		
	-	Janet	Milazzo
	_	0 2/1	7/86

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RZ-79
13 Week Sacrifice
Male Rats

£	Group C	Group H	Group L	Group M	
NASAL CAVITY-LEVEL I		: :			
(NO. EXAMINED)	(10)	(10)	(10)	(10)	
Serous Exudate	1	i			
Hemorrhage	2	2	5	2	
Submucosal Pigment Deposition		4			
. Nonsuppurative Rhinitis			. 1		
Hyperplasia of Goblet Cells	·	•	1		
Suppurative Exudate	·	: 		1	
Inflammation of Nasolacrimal					
Duct					_
	_				
NASAL CAVITY-LEVEL II					
(NO. EXAMINED)	(10)	(10)	(10)	(10)	
Serous Exudate	1				
. Hemorrhage	1	3	4	2	
Submucosal Pigment Deposition		10			
Inflammation of Nasolacrimal		:			
Duct		1	*		
Nonsuppurative Rhinitis			1		
Cystic Glands				1	
		- · - · · - · · -			
MASAL CAVITY-LEVEL III					
NO. EXAMINED)	(10)	(10)	(10)	(10)	
Hemorrhage	1	1	1	1	
Submucosal Pigment Deposition		10		3	
Nonsuppurative Rhinitis			1		
Cystic Glands			1	-	
Inflammation of Nasolacrimal		- - · · -	· · · · · · · · · · · · · · · · · · ·	•	- · ·
Duct			·		
	<u></u>		· — · · · · · · · · · · · · · · · · · ·		

RZ-79 13 Week Sacrifice Male Rats

	Group C	Group H	Group L	Group M	:	
NASAL CAVITY-LEVEL IV		1			·	
(NO. EXAMINED)	(10)	(10)	(10)	(10)		
Serous Exudate	1	:				
Hemorrhage	1		1			
Submucosal Pigment Deposition		10		5		
LIVER (NO. EXAMINED)	(10)	(10)		(10)		
Foci of Mononuclear Cells	5	6		3		
Bile Duct Hyperplasia		1		1		
Pigment Deposition		10				
Infarction				1		
KIDNEY (NO. EXAMINED)	(10)	(10)		(10)		
Regenerative Tubular						
Epithelium	3	8		5		
Casts	5	9	~	7		
Pigment Deposition	10	10		10		
Foci of Mononuclear Cells	4	8		4		
Tubular Mineralization		····	····			
Cyst						
LUNG (NO. EXAMINED)	(10)	(10)		(10)		_ · ·
Pigment Deposition		1				
Hyperplasia of Type II Cells		1				
Peribronchial Lymphoid						
Hyperplasia	8	9		10	-	
Accumulations of Foamy					··· ···	-
Macrophages		1			•	
		· 			<u>.</u>	·-

RZ-79 13 Week Sacrifice Male Rats

÷.	Group C	Group H	Group L	Group M	:
BRAIN (NO. EXAMINED)	(10)	(10)	1		
.		I			
PITUITARY (NO. EXAMINED)	(10)	(10)			
	/10)	(0)			·
ADRENAL (NO. EXAMINED)	(10)	(8)	 		
Vacuolated Cortical Cells	1				
EYE (NO. EXAMINED)	(10)	(10)			
Retinal Degeneration		1			
٦					
THYROID (NO. EXAMINED)	(10)	(10)			
*. 					
LARYNX (NO. EXAMINED)	(10)	(10)			
Foci of Mononuclear Cells		3			
TRACHEA (NO. EXAMINED)	(10)	(10)			
Foci of Mononuclear Cells		2			
LYMPH NODE, TRACHEOBRONCHIAL	_	<u> </u>			· · · · · · · · · · · · · · · · · · ·
(NO. EXAMINED)	(10)	(10)		 -	
Lymphoid Hyperplasia	1				
Hemorrhage				··	
Pigment Deposition		-			
		:			
HEART (NO. EXAMINED)	(10)	(10)			
Nonsuppurative Myocarditis	3	1			
Dilatation		1			
	•	!	- · <u>-</u>		
.;	: 			·	· ·

RZ-79 13 Week Sacrifice Male Rats

·	Group C	Group Group
SPLEEN (NO. EXAMINED)	(10)	(10)
PANCREAS (NO. EXAMINED)	(10)	(10)
Focal Acinar Atrophy		1
LYMPH NODE, POPLITEAL		
(NO. EXAMINED)	(10)	(10)
Pigment Deposition		2
Lymphoid Hyperplasia		
Hemorrhage		
STOMACH (NO. EXAMINED)	(10)	(10)
DUODENUM (NO. EXAMINED)	(10)	(10)
CECUM (NO. EXAMINED)	(10)	(10)
Nematodiasis	2	1
COLON (NO. EXAMINED)	(10)	(10)
Nematodiasis	1	
SKIN (NO. EXAMINED)	(10)	(10)
TESTIS (NO. EXAMINED)	(10)	(10)
EPIDIDYMIS (NO. EXAMINED)	(10)	(10)
		
	·	

TRZ-79
13 Week Sacrifice
Male Rats

	Group C	İ	Group H	Group L	Group M		
PROSTATE (NO. EXAMINED)	(10)	:	(10)				
							-
URINARY BLADDER (NO. EXAMINED)	(10)		(10)				
						·	
FEMUR (NO. EXAMINED)	(10)	_!_	(10)				
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EPL Experimental Pathology Laboratories, Inc

RZ-79 13 Week Sacrifice Female Rats

	Group C	Group H	Group L	Group M	
NASAL CAVITY-LEVEL I		i			
(NO. EXAMINED)	(10)	(10)	(10)	(10)	
Serous Exudate	1	!			
Hemorrhage	1		1	3	
Submucosal Pigment Deposition		4	-		
Nonsuppurative Rhinitis	2	2			
Hyperplasia of Goblet Cells		1			
Suppurative Exudate					
Inflammation of Nasolacrimal					
Duct			1	1	
NASAL CAVITY-LEVEL II					·
(NO. EXAMINED)	(10)	(10)	(10)	(10)	
Serous Exudate		1			
Hemorrhage	2		1		
Submucosal Pigment Deposition	-	10			
Inflammation of Nasolacrimal					
Duct	-		1		
Nonsuppurative Rhinitis	2	1		1	
Cystic Glands					
NASAL CAVITY-LEVEL III					
(NO. EXAMINED)	(10)	(10)	(10)	(10)	
Hemorrhage					-
Submucosal Pigment Deposition		10		2	
Nonsuppurative Rhinitis	-	<u> </u>	_		_
Cystic Glands	:	-		.	
Inflammation of Nasolacrimal	<u>.</u>	-	 	-	
Duct	···				

RZ-79 13 Week Sacrifice Female Rats

i.	Group C	Group H	Group L	Group M	
NASAL CAVITY-LEVEL IV		1			
L(NO. EXAMINED)	(10)	(10)	(10)	(10)	
Serous Exudate	·	• • • • • • • • • • • • • • • • • • •			
Hemorrhage		·	·	 	
Submucosal Pigment Deposition	· · · · · · · · · · · · · · · · · · ·	10		7	· · · · · · · · · · · · · · · · · · ·
L					
LIVER (NO. EXAMINED)	(10)	(10)	(10)	(10)	
Foci of Mononuclear Cells	4	3	3	6	
Bile Duct Hyperplasia				 	
Pigment Deposition		10		2	
Infarction					
: [
XIDNEY (NO. EXAMINED)	(10)	(10)	· · · · · · · · · · · · · · · · · · ·	(10)	
Regenerative Tubular	-	 	-· 		
Epithelium			· · · · · · · · · · · · · · · · · · ·		
Casts	11			11	
Pigment Deposition	8	10		10	
Foci of Mononuclear Cells	2	2		2	
Tubular Mineralization	10	10		10	
Cyst			.	1	
() 					
LUNG (NO. EXAMINED)	(10)	(10)	<u></u>	(10)	
Pigment Deposition		.	<u> </u>		
Hyperplasia of Type II Cells					
Peribronchial Lymphoid					
Hyperplasia	10	9	<u> </u>	9	
Accumulations of Foamy		<u>.</u>			•
Macrophages		•	· · · · · · · · · · · · · · · · · · ·		.
		_			·
<u> </u>	<u> </u>				

RZ-79 13 Week Sacrifice Female Rats

•	Group	Group H	Group L	Group M	:	
BRAIN (NO. EXAMINED)	(10)	(10)				
PITUITARY (NO. EXAMINED)	(10)	(10)	· · · · · · · · · · · · · · · · · · ·			
ADRENAL (NO. EXAMINED)	(10)	(10)	 	· 	· · · · · · · · · · · · · · · · · · ·	<u>}</u>
Vacuolated Cortical Cells						
EYE (NO. EXAMINED)	(10)	(10)				
Retinal Degeneration						
THYROID (NO. EXAMINED)	(10)	(10)				
LARYNX (NO. EXAMINED)	(10)	(10)				
Foci of Mononuclear Cells		1				E
TRACHEA (NO. EXAMINED)	(10)	(10)	,			
Foci of Mononuclear Cells		1		-		
LYMPH NODE, TRACHEOBRONCHIAL						
(NO. EXAMINED)	(9)	(8)				
Lymphoid Hyperplasia Hemorrhage	3	3			<u> </u>	
Pigment Deposition	4	2				
HEART (NO. EXAMINED)	(10)	(10)	-			
Nonsuppurative Myocarditis	2	1				
Dilatation						
				·-· —	· · · · ·	
						

RZ-79 13 Week Sacrifice Female Rats

,	: Group C	Group H	Group L	Group M			
SPLEEN (NO. EXAMINED)	(10)	(10)					
				:			
PANCREAS (NO. EXAMINED)	(10)	(10)					
Focal Acinar Atrophy	; 						
	·	· - 					
LYMPH NODE, POPLITEAL		· 		· · · ·			
(NO. EXAMINED)	(8)	(9)					
Pigment Deposition		1					
Lymphoid Hyperplasia	·	1			~ <u></u>		
Hemorrhage		1			~		
					- 		
STOMACH (NO. EXAMINED)	(10)	(10)					
							
DUODENUM (NO. EXAMINED)	(10)	(10)		· · · · · · · · · · · · · · · · · · ·	<u>.</u>		
					·		
CECUM (NO. EXAMINED)	(10)	(10)					
Nematodiasis			·			. <u></u>	
·						·····	
COLON (NO. EXAMINED)	(10)	(10)	 				
Nematodiasis	1						-
SKIN (NO. EXAMINED)	(10)	(10)	·				
UTERUS (NO EVALUACIONALISTA							-
UTERUS (NO. EXAMINED)	(10)	(10)					
Dilatation	1	2					
OVARY (NO. EXAMINED)	(10)	(10)					
		*		<u> </u>	· ·-	-	~
						-	
		•					
							

RZ-79 13 Week Sacrifice Female Rats

	Group C	Group H	Group	Group :	····	3
URINARY BLADDER (NO. EXAMINED)		(10)				
FEMUR (NO. EXAMINED)	(10)	(10)		<u> </u>		1
				····		
						
		•				
			 			
						_]
						E
			 -			
						
		_				2
						
					-	
		-			·. ·	

HISTOPATHOLOGY INCIDENCE TABLES

GROUP	CONCENTRATION
С	Control
L	Low Exposure Concentration
M	Medium Exposure Concentration
н	High Exposure Concentration

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주Z-79 汽3 Week Sacrifice Male Rats						Gr	oup	c				
	2 N I S B E	3 9 9 8 -	3 9 9 8 -	3 9 9 8 -	3 9 9 8	3 9 9 8	3 9 9 8	3 9 9 8	3 9 9 8	3 9 9 8 -	3 9 9 8 -	·
	L A	3	3	3 2	3	3 4	3 5	3	1 3 7	3	3	
ASAL CAVITY-LEVEL I		X	X	X	X	X	X		X	X		
Serous Exudate		[-				1	-			
Hemorrhage								1_			3	
Submucosal Pigment Depositio	n							- <u>-</u> -				
Nonsuppurative Rhinitis				·								
Hyperplasia of Goblet Cells								_		· -	_	
Suppurative Exudate												
<u>Inflammation of Nasolacrimal</u>						·			<u></u> -			
Duct		l				_			<u>.</u>	_		
<u> </u>				. <u>.</u> .			<u>-</u>					
ASAL CAVITY-LEVEL II		X	X	<u>X</u>	X	X	X		X	X		
Serous Exudate								1				
- Hemorrhage								_			3	
Submucosal Pigment Depositio	n	l								_		
. Inflammation of Nasolacrimal												
Duct					_							
Nonsuppurative Rhinitis												
Cystic Glands]										
-							-					
ASAL CAVITY-LEVEL III		X	X	X	X	X	X	X	X	X		•
Hemorrhage					•	-					2	
Submucosal Pigment Depositio									•			
Nonsuppurative Rhinitis	•								-			
Cystic Glands		- 1				•						· · · · · · · · · · · · · · · · · · ·
Inflammation of Nasolacrimal			· – .									
Duct		-										

11-1

EPL Experimental Pathology Laboratories, Inc.

Key P = Present N = NC Section
1 = Min ma: 2 + Stight
5 - Severe High | 1 - Incomplete Section

RZ-79 13 Week Sacrifice Male Rats	ĺ					Gr	oup	С				
•	A N U I M B A E L R	3 9 9 8 - 1 3 0	3 9 8 - 1 3	3 9 8 - 1 3 2	3 9 9 8 - 1 3	3 9 9 8 - 1 3 4	3 9 9 8 - 1 3 5	3 9 9 8 - 1 3 6	3 9 9 8 - 1 3 7	3 9 9 8 - 1 3 8	3 9 9 8 - 1 3	
NASAL CAVITY-LEVEL IV		_X	_X_	_X_	X,	X.	_X,		X	_X_	_	
												· · - - · · · · · · · · · · · · · · · · · ·
		J										
<u>Submucosal Pigment Depositi</u>					•							.
1												
		1										· · · · · · · · · · · · · · · · · · ·
1		l										
1		ł .										· · · · · · · · · · · · · · · · · · ·
		ļ										
KIDNEY		ı										
Regenerative Tubular		l										
1		J										•
Casts												
Pigment Deposition		1	1	1.	1_	1	1	1	1	1	1	
Foci of Mononuclear Cells		ļ		1	,1,		1,				1	
Tubular Mineralization		-								-		
Cyst				-			-					
LUNG	~	X_				•				-	Y	
Pigment Deposition		^-	-								. ^	
Hyperplasia of Type II Cell	s	1										
Peribronchial Lymphoid] -	•	•								
Hyperplasia	-		1	1	1	1	1	1	1	1		
Accumulations of Foamy					•						<u>.</u>	
Macrophages		<u> </u>										

11-2

EPL Experimental Pathology Laboratories, Inc

Key Paresent Name Se

1 = Mir. mal 2 = Sight 5 * Severe High 1 = Incomplete Section A Allayer Aminer Remarkable

3 - Moberate 4 - Moderately Severe

-RZ-79 R-13 Week Sacrifice Group C Male Rats X X X X X X X X X X ERAIN X X X X X X X X X X PITUITARY X X X X X X X X X **ADRENAL** Vacuolated Cortical Cells 1 - EYE Retinal Degeneration X X X X X X X X X THYROID X X X X X X X X X X LARYNX ... Foci of Mononuclear Cells TRACHEA____ ____ x x x x x x x x x x x Foci of Mononuclear Cells LYMPH_NODE, TRACHEOBRONCHIAL ____2 Lymphoid Hyperplasia Hemorrhage Pigment Deposition **→HEART** 2 2 1 Nonsuppurative Myocarditis Dilatation

11-3

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EPL Experimental Pathology Laboratories, Inc.

P = Present N = No Section
1 = Minima* 2 = Sight
5 = Severe High 1 = Incomplete Section

RZ-79 13 Week Sacrifice Male Rats	[Group C	
•	A N N U I M M B A E L R	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 9 9 9 9 9	
SPLEEN		3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 0 1 2 3 4 5 6 7 8 9 X X X X X X X X X X X X	
PANCREAS Focal Acinar Atrophy		<u>x_x_x_x_x_x_x_x_x_x_x_x_x_x_x_x_x_x_x_</u>	!
Pigment Deposition			
<u>Hemorrhage</u>			
		<u>, X., X., X., X., X., X., X., X., X., X.</u>	
		x x_, x_, x_, x_, x_, x_, x_, x_, x_,	
Nematodiasis		XP	
COLON Nematodiasis		_X _ X _ X _ X _ X _ X _ X _ X _ P	
SK1N		XX, X, X, X, X, X, X, X, X	
TESTIS		x x x x x x x x x x x x x x x x x x x	

11-4

Experimental Pathology Laboratories, Inc.

P = Present N = Nc Section

1 = Minimal 2 = Sight

5 = Severe High 1 = Incomplete Section

A = Autolysis A = Not Remarkable

3 = Moderate 4 = Moderatery Severe

₹₹Z-79 \$:3 Week Sacrifice Male Rats	•					Gr	ont	C C											•		
(3	3	3	3	3	3	3	3	3	3										
N N	AN NU IM MB	9	9 9 8	9 8						3 9 9 8	9 9 8										
*	A E L R	1 3 0	1 3 1	1 3 2	1 3 3			1 3 6		_	1 3 9										
PIDIDYMIS		X	_Х .	X	X.	X	X	X	X	_ X.	X		-					-			
PROSTATE		X	X	X	<u>X</u>	X	X	X	X	X	X		· · ·	; , - ·	-						
URINARY BLADDER		X	X	X	X	X	X	X	X	X	X				_						
FEMUR		_ X	X	X	X	X	X	Χ_	X	X	X										
						- · · - ·	-	·			~ -	 ·			• ···	•					
·									• •			-					- - .		<u>.</u> .	-	
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		L_																			

11-5

EPL Experimental Pathology Laboratories, Inc

Key P = Present N = Nc Section
1 = Minima* 2 = Sigh1
5 = Severe High 1 = Incomplete Section

RZ-79 13 Week Sacrifice Male Rats	[_	Gr	oup	н													7
- A N N U ! M M B A E L R	4 0 0 1 - 1 3 0	4 0 0 1 - 1 3 1	4 0 0 1 - 1 3 2	4 0 0 1 - 1 3 3	4 0 0 1 - 1 3 4	4 0 0 1 - 1 3 5	4 0 0 1 - 1 3 6	4 0 0 1 - 1 3 7	4 0 0 1 - 1 3 8	4 0 0 1 - 1 3 9										
NASAL CAVITY-LEVEL I	X			<u> X</u>					_ X .	X										
Serous Exudate									<u>-</u>		_									1.
Hemorrhage	J		3		1_				~ - <i>-</i> -			. <i>:</i>	· <u>· ·</u> _							-
Submucosal Pigment Deposition Nonsuppurative Rhinitis		_2_						-	-		-					-	- -	_		7
Hyperplasia of Goblet Cells																				1
Suppurative Exudate											<u>-</u>									
Inflammation of Nasolacrimal	J		. 	<u>-</u>														_		
Duct	_		.												•		_];
	1	-									-							٠.		
NASAL CAVITY-LEVEL II	J					-			-				-							. 5
Serous_Exudate	 											-	-			-				k
<u> Hemorrhage</u>		1.	. 2	-	1.															17
Submucosal_Pigment_Deposition	. 3.	. 1	.1.	1.	2.	2 ,	2	1	2	2_					-		-	-		۱.
Inflammation_of_Nasolacrimal						-		-									-			- ₹
Duct		···					2	-							-					
Nonsuppurative Rhinitis							-											-		:
Cystic Glands						-													-	+
)						-					-	-							
NASAL CAVITY-LEVEL III	-\ . -			.				. ~												'
Hemorrhage	1		.	_		1													-	
Submucosal Pigment Deposition	. 3.	3	3	2	3	3	3	3	3	2										}
Nonsuppurative Rhinitis	1	•	-										-							
Cystic_Glands																				:
Inflammation of Nasolacrimal		. ,				٠	٠					-	-	-						١.
Duct										-										

11-6

E P L Experimental Pathology Laboratories, Inc.

Key P-

P + Present N - No Section
1 + Mir.mal 2 - Sight
5 + Severe High 1 - Incomplete Section

Am A, to you ham N, ti Ferrarkable.
3 H Modinate - 4 H Modinate y Severe High

NZ-79 Neek Sacrifice Male Rats			_			Gr	oup	Н					
	A N U I M B A E L R	4 0 0 1 - 1 3 0	4 0 0 1 - 1 3 1	4 0 0 1 - 1 3 2	4 0 0 1 - 1 3 3	4 0 0 1 - 1 3 4	4 0 0 1 - 1 3 5	4 0 0 1 - 1 3 6	4 0 0 1 - 1 3 7	4 0 0 1 - 1 3 8	4 0 0 1 - 1 3 9		
HASAL CAVITY-LEVEL IV						-							
Serous Exudate		l						_]
Hemorrhage]
Submucosal Pigment Depositi	on	3	3	3	3	3_	4	3_	_3_	3	_3 .		
LIVER										· · · · · -			
Foci of Mononuclear Cells		1	1_	1_	2		1			_ 1			
Bile Duct Hyperplasia	·	2						-					
Pigment Deposition		1	1	1_	1	1	1	1	_1	1	1		
. Infarction											_		
<u> </u>													
KIDNEY		<u> </u>								.		· · · · · · · · · · · · · · · · · · ·	
Regenerative Tubular		ĺ		_									
Epithelium				2_	_2	.1	1_	2	_2	_1.	1_		
Casts			1	2	2	1	1	2_	2	2	1		
Pigment Deposition		3	3	3	3	3_	3	3	3	3.	3		
Foci of Mononuclear Cells		1	1	1		.1.	1		1	1	1		
Tubular Mineralization		<u> </u>						-					
L. Cyst		ļ. <u>.</u>											
		ļ								_			
LUNG		_	X		. ,	. <u>-</u>							
Pigment Deposition		_				,1							
Hyperplasia of Type II Cell	S			_		1							
Peribronchial Lymphoid													
Hyperplasia		1		1	1	1	1	1	1	1	1		
Accumulations of Foamy		ļ		· -					, ,				
Macrophages						_1_							

11-7

Experimental Pathology Laboratories, Inc.

P = Present N = No Section
1 = Minima* 2 = Sight
5 = Severe High 1 r fricomplete Section

RZ-79 Group H 13 Week Sacrifice Male Rats ٥ E BRAIN XXXXX X **PITUITARY** X X X X N X X X X N _____ **ADRENAL** Vacuolated Cortical Cells EYE Retinal Degeneration 3 THYROID LARYNX Foci of Mononuclear Cells 1 1 1 ____XXXXXXXXXXXX TRACHEA Foci of Mononuclear Cells ____ Lymphoid Hyperplasia Hemorrhage Pigment Deposition HEART Nonsuppurative Myocarditis Dilatation

11-8

EPL Experimental Pathology Laboratories, Inc.

Koy P-

P = Present N = No Section
1 = Minimal 2 = Siight
5 = Severe High 1 = Incomplete Section

13 Week Sacrifice Group H Male Rats j SPLEEN \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} **PANCREAS** Focal Acinar Atrophy LYMPH NODE, POPLITEAL Pigment Deposition Lymphoid Hyperplasia Hemorrhage **STOMACH** \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} DUODENUM **CECUM** X X X X X X X X X XNematodiasis COLON x x x x x x x x X X X Nematodiasis SKIN TESTIS

11-9

Experimental Pathology Laboratories, Inc

RZ-79

Kay P = Present N = No Section
1 = Minimal 2 = Sight
5 = Severe High 1 = Incomplete Section

Ale Autorysis — XIIII Not Remarkable 3 - Moderate — 4 - Mudiciately Severe Hig

RZ-79 13 Week Sacrifice Male Rats	Group H
- A N N U I M M B A E L R	4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4
EPIDIDYMIS	<u> </u>
PROSTATE	<u> </u>
URINARY BLADDER	<u> </u>
FEMUR	<u> </u>

11-10

EPL Experimental Pathology Laboratories, Inc.

Key P = Present
1 = Minima
5 = Solere Hi

N=No Section
2 = Slight
1 = Incomplete Section

A = Autolysis | X = Not Remarkable | 3 = Moderate | 4 = Moderate y Severe High

- RZ-79 13 Week Sacrifice Group L Male Rats A E NASAL CAVITY-LEVEL I Serous Exudate 1 1 4 1 1 Hemorrhage Submucosal Pigment Deposition Nonsuppurative Rhinitis Hyperplasia of Goblet Cells _ Suppurative Exudate Inflammation of Nasolacrimal Duct NASAL CAVITY-LEVEL II Serous Exudate 1 2 3 Hemorrhage Submucosal Pigment Deposition Inflammation of Nasolacrimal Duct Nonsuppurative Rhinitis Cystic Glands NASAL CAVITY-LEVEL III X X X X X X Hemorrhage Submucosal Pigment Deposition Nonsuppurative Rhinitis Cystic Glands Inflammation of Nasolacrimal Duct

11-11

EPL Experimental Pathology Laboratories, Inc.

P = Present N = No Section

1 = Minimal 2 = Sight

5 = Severe high I = incomplete Section

RZ-79 13 Week Sacrifice Male Rats	Ī					Gro	oup	L —										
A N ! N A L	M B E	3 9 9 - 1 3 0	3 9 9 - 1 3 1	3 9 9 - 1 3	3 9 9 - 1 3 3	3 9 9 - 1 3 4	3999-135	3 9 9 - 1 3 6	3 9 9 - 1 3 7	3 9 9 - 1 3 8	3 9 9 - 1 3 9							
NASAL CAVITY-LEVEL IV		X	X		X.	X	X	X	X	X	_X .		~	·				
Serous Exudate										_	_		_]
Hemorrhage				1_					~- -		-							
Submucosal Pigment Deposition	<u> </u>															·· <u>·</u>		
					·		-											
							<u>.</u> .		-									
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11-12

Experimental Pathology Laboratories, Inc

Key P = Present N = No Section

1 - M r.ma 2 + Sight
5 = Severe High 1 = Incomplete Section

같-79 첫 Week Sacrifice Male Rats						Gr	oup	M			
K			A	4					4	Δ	A
A N N N N N N N N N N N N N N N N N N N	N U M B E R	0 0 0 - 1	0000	0 0 0 - 1	0000	0 0 0 - 1	0 0 0 - 1	0 0 0 - 1	0 0 0 - 1	000	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
i i		3	3	3 2	3	3 4	3 5	3	3 7	3 8	3 9
ASAL CAVITY-LEVEL I		X	X	X	X		X		X _	Χ	
Serous Exudate					.	-					
Hemorrhage					·-	_2_		2			
Submucosal Pigment Deposition	<u> </u>							<u>-</u>			
Nonsuppurative Rhinitis										-	error en
Hyperplasia of Goblet Cells											
.Suppurative Exudate		l — —								-	. 1
Inflammation of Nasolacrimal									·		
Duct	:					- -				-	
<u> </u>						-			-	-	
NASAL CAVITY-LEVEL II		<u> </u>	X		. X .	<u>_X</u> .	- X _	<u>-</u>	X .	X _	X
- Serous Exudate				٠.							
- Hemorrhage				_1				_1			
Submucosal Pigment Deposition						- · ·					
Inflammation of Nasolacrimal	-							-			er e e e
Duct			. .				_			<u>.</u>	
Nonsuppurative Rhinitis											
Cystic Glands				_ 1		_					<u> </u>
<u>. </u>		_									
MASAL CAVITY-LEVEL III		X_			X	X			X	X.	X
Hemorrhage	-	_		-				1			
Submucosal Pigment Deposition	n		1	1			1				
Nonsuppurative Rhinitis				_							
Cystic Glands	_	 							-		
Inflammation of Nasolacrimal		.									
Duct											<u>. </u>
Ľ											
<u> 7-</u>											

II-13

EPL Experimental Pathology Laboratories, Inc.

P = Present N = No Section
1 = Minima* 2 = Sight
5 = Severe High 1 = incomplete Section

GROUP	CONCENTRATION
С	Control
L	Low Exposure Concentration
M	Medium Exposure Concentration
H	High Exposure Concentration

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_RZ-79 - 3 Week Sacrifice Male Rats	ļ					Gr	oup	M				
A N I N A L	N U M B E R	4 0 0 0 - 1 3 0	4 0 0 0 - 1 3 1	4 0 0 0 - 1 3 2	4 0 0 0 - 1 3 3	4 0 0 0 - 1 3 4	4 0 0 0 - 1 3 5	4 0 0 0 - 1 3 6	4 0 0 0 - 1 3 7	_	4 0 0 0 - 1 3 9	·
NASAL CAVITY-LEVEL IV		X			X_	<u>X</u>		X.	<u>X</u>			
- Serous Exudate			-							-	· - •	
<u>Hemorrhage</u>												
Submucosal Pigment Deposition	<u>1</u>		1	1			1					
IVER		X	X			<u>X</u>		X		_X_	X_	
Foci of Mononuclear Cells				_1_								
Bile Duct Hyperplasia												
Pigment Deposition												
KIDNEY												
Regenerative Tubular												
<u>Epithelium</u>				1.	2				3	1.	.1.	
Casts			1	. 1_	. 2_	1.	1	1.			_ 1	
Pigment Deposition		2_	1	1	_2	1	, 1	1	2	2	2	
Foci of Mononuclear Cells		1.	1_				1		. 1			
												· · · · · · · · · · · · · · · · · · ·
Cyst												
LUNG					- · - ·	·		- 				
Pigment Deposition												
<u>Hyperplasia of Type II Cells</u>		١			-		•					
Peribronchial_Lymphoid												
Hyperplasia		1_	1	1	. 1	1	. 1	1	1	1	1	
Accumulations of Foamy												
Macrophages		l										

11-14

EPL Experimental Pathology Laboratories, Inc.

P - Present N - No Section
1 - Minima* 2 + 5 go*
5 - Severe High 1 in Incomplete Section

A = Autoryold | X = N | 1 Remarkable | 3 = Modition | 4 = M | 1 alony Severe High

RZ-79 13 Week Sacrifice Group C Female Rats 9 U M B NASAL CAVITY-LEVEL I Serous Exudate Hemorrhage Submucosal Pigment Deposition Nonsuppurative Rhinitis Hyperplasia of Goblet Cells Suppurative Exudate Inflammation of Nasolacrimal Duct NASAL CAVITY-LEVEL II Serous Exudate Hemorrhage Submucosal Pigment Deposition Inflammation of Nasolacrimal Duct Nonsuppurative Rhinitis Cystic Glands NASAL CAVITY-LEVEL III **x x x x x x** Hemorrhage Submucosal Pigment Deposition Nonsuppurative Rhinitis Cystic Glands Inflammation of Nasolacrimal Duct

11-15

EPL Experimental Pathology Laboratories, Inc.

1 - Minima! 2 = Sligh! 5 = Severe High 1 = Incomplete Section

N = No Section

X = Not Remarkable
4 = Moderato y Severe High A ·· Autolys s 3 = Moderate

	A N							_				
¥ •	N U I M B A E L R	3 9 9 8 - 6	3 9 9 8 -	3 9 9 8 - 6	-	3 9 9 8 - 6	-	-	-	3 9 9 8	-	
		3	3	3	3	3	3	3	3	3	3	
MASAL CAVITY-LEVEL IV		X	X	X	<u>X</u> .	X	Χ.		X			
Serous Exudate												
Hemorrhage						- -						
Submucosal Pigment Deposit	on									. 		
							- -				<i>-</i>	
IVER			<u>X</u>			<u>X</u> .	<u>X</u>	<u>X</u> .	<u>X</u> .	<u>X</u> _	- -	
Foci of Mononuclear Cells		1_		1	.1_						1.	
Bile Duct Hyperplasia		<u> </u>					.	~ .		-		
Pigment Deposition											<u> </u>	
Infarction							. <u></u> -	- •				
												·
IDNEY		l										·· - · · · · · · · ·
Regenerative Tubular												
												
Casts						. 1 .		· - —				
Pigment Deposition					1.	1.	_	-		1	1.	
Foci_of_Mononuclear_Cells					_1_		1.					
Tubular Mineralization		3_	_2 _	_3_	.2_	3	3 _	3	2	3	. 2 .	
Cyst						•	•			-		
			- ·		-	-		-		-		
UNG		~ -									-	
Pigment Deposition		·	· - ·			-	•	-				
Hyperplasia of Type II Cell	15		٠	-	• •		,	•				
Peribronchial Lymphoid Hyperplasia		-		1	 1			,	1	1	1	
Accumulations of Foamy		•		1.	1,	١.	ī	١.	1 .	1	1,	
Macrophages		-				-			-	-		with the second

11-16

EPL P = Present N = No Section
1 = Minimal 2 = Slight
5 = Severe High I + Incomplete Section Experimental Pathology Laboratories, Inc.

RZ-79 13 Week Sacrifice Group C Female Rats 6 BRAIN X X X X X PITUITARY x x x x x x x x x x x ADRENAL Vacuolated Cortical Cells EYE Retinal Degeneration THYROID X X X X X X X X X X LARYNX Foci of Mononuclear Cells **TRACHEA** Foci of Mononuclear Cells LYMPH NODE, TRACHEOBRONCHIAL Lymphoid Hyperplasia Hemorrhage Pigment Deposition HEART Nonsuppurative Myocarditis

11-17

EPL Experimental Pathology Laboratories, Inc.

Dilatation

P = Present N = No Section

1 = Minimal 2 = Slight

5 = Severe High 1 = Incomplete Section

だZ-79 込3 Week Sacrifice Female Rats					Gr	oup	С				
A N I N I N I N I N I N I N I N I N I N	8 -	3 9 9 8 - 6	3 9 9 8 - 6	3 9 9 8 -		_		3 9 9 8 -	3 9 9 8 -	3 9 9 8 - 6	
	3	3	3	3	3	3	3	3	3	3	
PLEEN	_X_	_X_	Χ.	X	X	X	X	Ϋ́	Χ.	X	
ANCREAS	X	X	X	<u>X</u>	X	X	X_	X	X	X	
Focal Acinar Atrophy	1					— - - — -					
YMPH NODE, POPLITEAL Pigment Deposition	N	. X	_X _								
Lymphoid Hyperplasia Hemorrhage		<u> </u>	 ,				. <u>-</u>				
STOMACH				X					-	٠.	
<u> </u>	<u> </u>				-						
					· · - •						· · · · · · · · · · · · · · · · · · ·
Nematodiasis			X .	<u>X</u> .	X .	, X ,	, X _	X 	X	X	
COLON	l l			 . ₋ -							
Nematodiasis											<u>.</u>
-KIN	_ X			X	X	X	X.	X.		X	
IITERUS Dilatation	X			X	X	X	X		X	X	
	. -			. -		. ,					· · · · · · · · · · · · · · · · · · ·
					·						

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EP L

Experimental Pathology Laboratories, Inc.

Key P

P = Present N = N = N = Section
1 = M rimal 2 = S pht
5 = Severe High I = incomplete Section

RZ-79 13 Week Sacrifice Female Rats						Gr	oup	C									_				î S
	A N N U	3 9 9	3 9 9 8	3 9 9 8	3 9 9	3 9 9	3 9 9	3 9 9 8	3 9 9 8	3 9 9 8	3 9										19
	I M M B A E L R	9 8 - 6 3	9 8 - 6 3	9 8 - 6 3	9 8 - 6 3	9 8 - 6 3	9 8 - 6 3 5	9 8 - 6 3	9 8 - 6 3	9 8 - 6 3	9 8 6 3			•							3.5
OVARY		0	<u>1</u> X	2	3_	4		6	7		9	. <u></u>				<u> </u>				_	Į.
URINARY BLADDER		X	_ X _	X	X	X	_ X	X	X	_ X_	X		· · · ·		<u>-</u>	_ 					1 5
FEMUR		X	X	_x	<u>X</u>	X	X	X	X	X	X			- - · ·							
								<u>-</u>					<u>.</u>		. <u>-</u>		·				
								 -			<u>-</u>	 · ·-	-					- · -		-	-
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					 -	<u>.</u>					 -			<u>. </u>		-					
				• • •	-	-		<u> </u>	<u> </u>	•						<u>-</u> .	÷	•			
	–				-	-		-		-											
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			• • •		-		-	-						-	-						
		1			11-																ر : :

EPL Experimental Pathology Laboratories, Inc.

Key P ~ Present N = No Section
1 ~ Minima* 2 ~ Sight
5 ~ Severe High 1 ~ Incomplete Section

RZ-79 13 Week Sacrifice Female Rats						Gr	oup	Н									
	A N U I M B	4 0 0 1		-													
	A E L R	6 3 0	6 3 1	6 3 2	6 3 3	6 3 4	6 3 5	6 3 6	6 3 7	6 3 8	6 3 9						
NASAL CAVITY-LEVEL 1			X				_X_			_X	X					·• -	
Serous Exudate		ļ 		-									., 				
Hemorrhage					_												
Submucosal Pigment Depositi	on	1_		.1				_					- -				
Nonsuppurative Rhinitis					1			3			-			<u>-</u>	–		
Hyperplasia of Goblet Cells								3		- -					• • • •		
Suppurative Exudate Inflammation of Nasolacrima Duct	1	 						· ·		· -							
Ducc		-				• •			- •	·	·-·				•	· -	
NASAL CAVITY-LEVEL II										-				• •			
Serous Exudate						•		1	•	_ · -			*		•		
Hemorrhage																	
Submucosal Pigment Depositi	on	2	2	2	2	2	2	2	2	2	_2						
Inflammation of Nasolacrima Duct	1			.	.							_		-			
Nonsuppurative Rhinitis		Ī					_	2									
_ Cystic Glands								_	_								
F		│							,								
NASAL CAVITY-LEVEL III Hemorrhage		1			<u>.</u> .												-
Submucosal Pigment Depositi	on	3	4	3	3	3	3	3	3	3	3						
Nonsuppurative_Rhinitis																	
Cystic_Glands											•						
Inflammation of Nasolacrima	1																.
μ Duct																÷	
<u> </u>		<u> </u>															

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EPL Experimental Pathology Laboratories, Inc.

P = Present N = No Section

1 = M c.ma 2 = Slight

5 = SevereHigh 1 = Incomplete Section

All Authors All Not Remarkable 3 - Moderately Severe High

RZ-79 13 Week Sacrifice Female Rats	1					Gr	oup	H											
	A N U I M B A E L R	4 0 0 1 - 6 3 0	4 0 0 1 - 6 3 1	4 0 0 1 - 6 3 2	4 0 0 1 - 6 3 3	4 0 0 1 - 6 3 4	4 0 0 1 - 6 3 5	4 0 0 1 - 6 3 6	4 0 0 1 - 6 3 7	4 0 0 1 - 6 3 8	4 0 0 1 - 6 3 9								
NASAL CAVITY-LEVEL IV															-				
Serous Exudate																	. .		
Hemorrhage												· · 	<u> </u>						
Submucosal Pigment Deposition	ก	3	4	4_	3_	3_	3	3_	3	3 _	. 3 .								
								- -											
LIVER											٠.				-				
Foci of Mononuclear Ceils		1_1_	_1_			- -				1	-	· —·	·- -				·	·	
Bile Duct Hyperplasia		-											-	_	• •				
Pigment Deposition		1	· <u>2</u> .	. 2	2	1.	. 1	.1	1	1 _	.1 .	• • •				•			
Infarction				-						-				-					
KIDNEY											-								_ 1
Regenerative Tubular									_			_							
Epithelium														. <u></u> .			-		
Casts													-		_		•	_	
Pigment Deposition		3	3	3	3	3	3	3	3	3	3 _			_					
Foci of Mononuclear Cells]		<u> </u>	1		. 1							_					
Tubular Mineralization	-	2	3	1	. 2	2	3_	2	3	2	3								
Cyst			•				-												
					_		-		-			÷							
LUNG	- ·					-	. Х												٠
Pigment Deposition																			
Hyperplasia of Type II Cell	S .	ļ	-			-	-												
Peribronchial Lymphoid	-	} .				-									-				
Hyperplasia		1.	1	. 1	. 1	. 1	-	1	1	. 1	1		-	-					-
Accumulations of Foamy		┨ -	- -		-	•	•				-	•							
Macrophages		<u> </u>	-																

EPL Experimental Pathology Laboratories, Inc.

N - No Section
2 - Slight
I m Incomplete Section

	HISTOPATHOLOGY INCIDENCE TABLE	
AZ-79 A3 Week Sacrifice Female Rats	Group H	
	A N O O O O O O O O O O	
288	N U O O O O O O O O O O O O O O O O O O	
	1 R 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6	
RAIN	X X X X X X X X X X X X X X X X X X X	
PITUITARY	<u> </u>	
ADRENAL Vacuolated Cortical Cells	<u> </u>	_
:YE Retinal Degeneration	<u> </u>	
THYROID	<u>x_x_x_x_x_x_x_x_x_x_x_x_x_x_x_x_x_x_x_</u>	-
ARYNX Foci of Mononuclear Cells	X_X X X X X X X X X X X X X X X X X X X	
TRACHEA - Foci of Mononuclear Cells	<u>x x x x x x x x x x x x x x x x x x x </u>	- ;
YMPH_NODE, TRACHEOBRONCHIAL Lymphoid Hyperplasia Hemorrhage		
Pigment Deposition		

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_ . . _ X _ X . X .

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Nonsuppurative Myocarditis

HEART_

Dilatation

Key + Present N = No Section
1 + Mirimal 2 - Sight
5 - Severe High 1 + Incomplete Section

A = Autolysis | X = N. I Femarkable 3 - Moderate | 4 = M. Derately Severe High

R2-79 13 Week Sacrifice Female Rats		<u> </u>				Gr	oup	H			·-										
•	A N U I M B A :	4 0 0 1 - 6 3 0	4 0 0 1 - 6 3 1	4 0 0 1 - 6 3 2	4 0 0 1 - 6 3 3	4 0 0 1 - 6 3 4	4 0 0 1 - 6 3 5	4 0 0 1 - 6 3 6	4 0 0 1 - 6 3 7	4 0 0 1 - 6 3 8	4 0 0 1 - 6 3 9										5555
SPLEEN		X	X	X	X	X	X	X	X	X	Χ_		~				-		-		13
PANCREAS Focal Acinar Atrophy		X	X	X	<u>X</u>	<u>X</u>	X	X_	X	X	X		· ·		-		-		·		12.
LYMPH NODE, POPLITEAL Pigment Deposition Lymphoid Hyperplasia Hemorrhage		2	1	X	X	<u>X</u>	X .	X _	X _	N_	X				- - -		- ·	- · ·	- · · · · · · · · · · · · · · · · · · ·		2
STOMACH		X	X	X	_ X	X	X	X	X	. X	X					•	 - -				
DUODENUM		X	X	X	X	 . X	X	X	X	X	X					. .				- <u>-</u>	
CECUM Nematodiasis		X	X	X	 . X .	X	. X	X .	X	X	X				-		-		-		
COLON Nematodiasis		X	X	X	. X	X	X	X	X	X	X			÷							
SKIN		X	X	X	. X	X	X	X	X	X	X	-		٠							
UTERUS Dilatation		X	X	X	- X	X	. X	X		X	3		•								
		1			-		-	•					- •	•							

スRZ-79 【13 Week Sacrifice 「Female Rats	Group H
A N U I M M B A E L R	4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4
OYARY	<u>x_x_x_x_x_x_x_x_x</u>
URINARY BLADDER	<u> </u>
FEMUR	<u> </u>
·	
	· · · · · · · · · · · · · · ·
\\.\.\.\.\.\.\.\.\.\.\.\.\.\.\.\.\.\.\	
J	
<u> </u>	

11-24

EPL Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section
1 = Micimal 2 = Sight
5 = Severe High 1 = Incomplete Section

A = Autoysis — Allerty C Bend Kable 3 r Mode ato — 4 r Miccourtely Severe High

RZ-79 13 Week Sacrifice Female Rats		ر -				Gr	oup	ι 													- ;
	A N N U I M M B A E L R	3 9 9 - 6 3 0	3 9 9 - 6 3	3 9 9 - 6 3 2	3 9 9 - 6 3 3	3999-634	3999-635	3 9 9 - 6 3 6	3 9 9 - 6 3 7	3999-638	3 9 9 - 6 3 9				-						
NASAL CAVITY-LEVEL I		<u>X</u>	X		X	X	X	X	X												-
Serous Exudate		ļ			<u> </u>						- - .			-,		-					
Hemorrhage				1										´_			_				
Submucosal Pigment Deposition	n	L										-	_								
Nonsuppurative Rhinitis		 										. .									
Hyperplasia of Goblet Cells		ļ														_					
Suppurative Exudate		↓												_	_						
Inflammation of Nasolacrimal		ļ												_			<u>-</u>				
Duct							_			,	. 1		-	-				-	-	- - ,	
NASAL CAVITY-LEVEL II		X	X		X	X	X	X	X	X		_					_	-	-		
Serous Exudate		<u> </u>						_						_							
Hemorrhage		<u> </u>		1	_																
Submucosal Pigment Deposition Inflammation of Nasolacrimal					-						.			-					-		
Duct		1									2			-		•				-	1
Nonsuppurative Rhinitis		1	•	•			•							-							1
Cystic Glands		1					-													٠	
		1		-	•			•		•	-			-	·						
NASAL_CAVITY-LEVEL_IIIHemorrhage		1			X	X	X	X	X	X											
Hemorrhage Submucosal Pigment Deposition				-																	
Nonsuppurative Rhinitis					-	•									-						
]			-																
Cystic Glands Inflammation of Nasolacrima	 I	1	-	•	-	•	•							-	•						
Duct		1							-		2				•						
		┥ …		-	-		-							-		-		-			1

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EPL Experimental Pathology Laboratories, Inc.

P = Present N = No Section
1 = Minima* 2 = Sight
5 = Severe High I = Incomplete Section

A = Autolysis 3 = Moderate

-RZ-/9 -13 Week Sacrifice -Female Rats	ſ					Gr	oup	L					 	-	 	-	
	A N N U I M M B A E L R	3 9 9 - 6 3 0	3999-631	3999-632	3999-633	_	3 9 9 - 6 3 5	_	_	3999-638	3999 - 639						
NASAL CAVITY-LEVEL IV Serous Exudate Hemorrhage Submucosal Pigment Depositio	n									· · · <u></u>			 ;=-		 		
Foci of Mononuclear Cells Bile Duct Hyperplasia Pigment Deposition Infarction			1	_X	<u>X</u>	X	<u>X</u>	X	1	X	1						
																	 -

11-26

E P L Experimental Pathology Laboratories, Inc.

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Key ProPlesent Non-Section
1 - Minimal 2 - Signt
5 - Severe High 1 - Incomplete Section

A - Autoyes - X = Not Remarkable

3 - Moderate - 4 = Moderately Severe in gh

RZ-79 13 Week Sacrifice Group M Female Rats NASAL CAVITY-LEVEL I Serous Exudate Hemorrhage Submucosal Pigment Deposition Nonsuppurative Rhinitis Hyperplasia of Goblet Cells Suppurative Exudate Inflammation of Nasolacrimal Duct NASAL CAVITY-LEVEL II Serous Exudate Hemorrhage Submucosal Pigment Deposition Inflammation of Nasolacrimal Duct Nonsuppurative Rhinitis Cystic Glands NASAL CAVITY-LEVEL III Hemorrhage Submucosal Pigment Deposition 1 Nonsuppurative Rhinitis Cystic Glands

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EPL Experimental Pathology Laboratories, Inc.

Inflammation of Nasolacrimal

Duct

Key P = Present 1 = Minimal 5 = Severe Hi N = No Section
2 = Stight
1 = Incomplete Section

A - Autolysis X - Not Remarkable
3 - Moderate 4 - Moderately Severe

RZ-79 13 Week Sacrifice Female Rats	_				Gr	oup	M					
A N I M A L	N ()	1 4 0 0 0 0 1 6 6 6		4 4 4 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	4 0 0 0 - 6 3 4	4 0 0 0 - 6 3 5	4 0 0 0 - 6 3 6	4 0 0 0 - 6 3 7	4 0 0 0 - 6 3 8	4 0 0 - 6 3 9	·	
NASAL CAVITY-LEVEL IV							X		I			
Serous Exudate												
Hemorrhage										.		_
Submucosal Pigment Deposition	1	<u> </u>		1_1	_ 1	_1_		_1_	_	1_		$\frac{1}{2}$
KIDNEY Regenerative Tubular				1		1	1.	1_	1	. X		
Epithelium						•						\dashv
Pigment Deposition Foci of Mononuclear Cells Tubular Mineralization Cyst		2 . 7	 2		. 2	. 2	3		2	1 1 2		
				-				• • •				
LUNG		 -		Χ	<u>.</u>			-				-
Pigment Deposition				 -				•	. ,			1
Hyperplasia of Type I1 Cells Peribronchial Lymphoid Hyperplasia			-			•	 	. 1	 	. 1		
Accumulations of Foamy	1	<u> </u>			 	<u>.</u>						
<u>Macrophages</u>												

11-28

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Key P = Present N = No Section
1 = Mirima
5 = Severe*High | J = Incomplete Section

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES

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5.53

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

| 1988年 | 1989年 | 19

Rats

Species

Males Sex.

Group Number C - Sacrificed

Dosage Level: Control,

?

Microscopic Observations	Lymphoid hyperplasia						·		
Client's Gross Observations	Enlarged 1+, redLymph								
Client's Tissue Identification	Tracheobronchial lymph node								
Animal Number	3998-131								

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

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Dosage Level: High Exposure H - Sacrificed Group Number Males ž Species Rats

Anmal	Client's Tissue Identification	Client's Gross Observations	Microscopic Observations
4001-130	Skin	Yellow	No corresponding lesion
	Popliteal lymph node	Reddened moderate	No_corresponding lesion
	Lung	Minimal yellow pigment	No corresponding lesion
4001-131	Popliteal lymph node	Right, pink color	No_corresponding lesion
	Lung	Minimal_yellow_pigment	No_corresponding_lesion
4001-132	Skin	Yellow	No corresponding leston
	Popliteal lymph node	Moderate dark gray	Pigment deposition
	Lung	Pigment yellow minimal	No corresponding leston
	Heart	Rounded and enlarged	Dilatation
4001-133		Yellow	No corresponding leston
i	Popliteal lymph node	Moderate dark gray	Pigment deposition
	Lung	Pigment yellow minimum	No corresponding leston
4001-134	Skin	Yellow	No corresponding leston
	Popliteal lymph node	Gray, mild	No corresponding lesion
	Lung	Minimal yellow	pigment deposition; hyperplasia
 			or type 11 certs
4001-135	Skin	Yellow	No corresponding lesion

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27.2

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Sex: Males

Species Rats

Group

Group Number H - Sacrificed

Dosage Level: High Exposure

3

3

4001-136 (cont. d) Popliteal lymph node Gray NO corresponding lesion 4001-136 (stin) Yellow Pigment, yellow, minimal NO corresponding lesion 4001-137 (stin) Pigment, yellow, minimal NO corresponding lesion 4001-138 (stin) Yellow No corresponding lesion 4001-138 (stin) Yellow No corresponding lesion 4001-139 (stin) Yellow No corresponding lesion 4001-139 (stin) Yellow No corresponding lesion 4001-139 (stin) Yellow No corresponding lesion	Animal	Client's Tissue Identification	Client's Gross Observations	Microscopic Observations
Skin Yellow minimal Lung Pigment, yellow minimal Lung Yellow Lung Winimal yellow pigment Skin Yellow Lung Minimal yellow pigment Lung Minimal yellow pigment	4001-135 (Cont'd)	1 1	Gray	No corresponding lesion
Lung Skin Lung Skin Lung Skin Lung Skin Minimal yellow pigment Lung Skin Minimal yellow pigment Minimal yellow pigment Lung Skin Minimal yellow pigment		Lung	Pigment, yellow, minimal	No corresponding lesion
Skin vellow minimal Lung pigment, yellow minimal Skin vellow Minimal yellow pigment Lung Minimal yellow pigment Lung Minimal yellow pigment	4001-136	1	Yellow	No corresponding leston
Lung Lung Lung Lung Lung Minimal yellow pigment Lung Minimal yellow pigment		Lung	Pigment, yellow, minimal	No corresponding lesion
Skin vellow Minimal yellow pigment Lung Minimal yellow pigment Lung Minimal yellow pigment Minimal yellow pigment	4001-137		Yellow	No corresponding lesion
Lung Lung Minimal yellow pigment Lung Minimal yellow pigment		Lung	Pigment, yellow, minimal	No corresponding lesion
Skin Yellow pigment Lung Minimal yellow pigment	4001-138		Yellow	No corresponding leston
Lung Minimal yellow pigment			Minimal yellow_pigment	No corresponding lesion
Minimal yellow pigment	4001-139		Yellow	No corresponding lesion
		Lung	Minimal yellow pigment	No corresponding lesion
	: 			

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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

M - Sacrificed

Group Number

Males

Ş

Rats

Species

Medium Exposure

Dosage Level:

Peribronchial Jymphoid hyperplasia Microscopic Observations Infarction Mass, rounded, yellowish tan, firm adhered to diaphragm Client's Gross Observations Pale foci 1+ Client's Tissue Identification 4000-137 Liver Lung 4000-139 Animal Number

111-4

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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species: Rats

Sex: Females

Group Number: C - Sacrificed

Dosage Level: Control

4.6

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Microscopic Observations	No corresponding lesion	No corresponding lesion								
Client's Gross Observations	Large 2+, red 1+	Enlarged 1+, red 1+						•		
Client's Trssue Identification	Tracheobronchial lymph node									
Animal	3998-634	3998-639								

RZ-79 13 Week Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

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Rats

Species

Females Š

Group Number H - Sacrificed

Dosage Level: High Exposure

Client's Tissue Identification Client's Gross Observations	Yellow No corresponding leston	node Left red, right gray Lymphoid hyperplasia	Minimal yellow pigment No corresponding lesion	Minimal yellow pigment No corresponding lesion	Yellow No corresponding lesion	lymph node Reddened Hemorrhage	Minimal yellow pigment No corresponding lesion	node Gray No corresponding leston	Yellow No corresponding lesion	Minimal yellow pigment No corresponding lesion	Minimal yellow pigment No corresponding lesion	Yellow No corresponding lesion	lymph node Reddened Hemorrhage	Minimal yellow pigment No corresponding lesion		Minimal yellow pigment No corresponding lesion	
	Skin	Popliteal lymph node Left	Lung	Lung	Skin	Tracheobronchial lymph node Redd	Lung	Popliteal lymph node Gray	Skin	Lung	Lung	Skin	Tracheobronchial lymph node Redd	Lung	Leng Minfe		Skin
Animal Number	4001-630		,	4001-631	4001-632			4001-633 P	4001-634		4001-635 L	4001-636			4001-637		. :

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RZ-79
13 Week Sacriffice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

A CHEST OF SECTION OF SECTION OF SECURITY
Species Rats

Sex Females

Group Number: H - Sacrificed

Dosage Level: High Exposure

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Animal	Client's Tissue Identification	Client's Gross Observations	Microscopic Observations
4001-639	Lung	Minimal yellow pigment	No. corresponding lesion
			-

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RZ-79 13 Week Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Sex: Females

Rats

Species

Group Number M - Sacrificed

Dosage Level: Medium Exposure

Peribronchial lymphoid hyperplasia Peribronchial lymphoid hyperplasia Microscopic Observations Client's Gross Observations Pink gray, white foci Pale_foci_1+ Client's Tissue Identification 4000-630 Lung 4000-637 Lung Animal Number

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RZ-79 17 Week Sacrifice Male Rats

•	Group C	Group H	Group L	Group M		
NASAL CAVITY-LEVEL I	ı	!	i			
(NO. EXAMINED)	(9)	(10)	(10)	(10)		
Hemorrhage	3	5	1	1	1	
Submucosal Pigmert Deposition	:	1			i	
Nonsuppurative Rhinitis	:	1		11		
Hyperplasia of Goblet Cells		i 1		2		
Cystic Glands				2		
NASAL CAVITY-LEVEL II		<u></u>			<u></u>	
(NO. EXAMINED)	(10)	(10)	: (10)	(10)	·	
Hemorrhage	3	2		2		
Submucosal Pigment Deposition		10				
Nonsuppurative Rhinitis		1		2		
Foreign Body						
NASAL CAVITY-LEVEL III		· 			-	
(NO. EXAMINED)	(10)	(10)	(10)	(10)		
Hemorrhage	1	2	1			
Submucosal Pigment Deposition		10		2		
Nonsuppurative Rhinitis		1				
NASAL CAVITY-LEVEL IV	- -	: :			·	
(NO. EXAMINED)	(10)	(10)	. (10)	(10)		
Submucosal Pigment Deposition		10	:	. 7		
Hemorrhage	:	3		!		
Suppurative Exudate	:	1		··		
	· · · · · · · · · · · · · · · · · · ·	<u> </u>				· · •
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RZ-79 17 Week Sacrifice Male Rats

	Group C	Group H	Group L	Group M	ŗ
LIVER (NO. EXAMINED)	(10)	(10)		(10)	
Foci of Mononuclear Cells	2	8		2	
Pigment Deposition	!	10		·	'
Bile Duct Hyperplasia	i	· · · · · · · · · · · · · · · · · · ·	·		
	<u>i</u>	·	·		
KIDNEY (NO. EXAMINED)	(10)	(10)		(10)	
Pigment Deposition	10	10		10	
Regenerative Tubular	· 	.			
Epithelium	9	10		7	
Casts	. 1	10	<u>.</u>	9	
Foci of Mononuclear Cells	4	8		6	
Cyst	·	1			
Tubular Mineralization	- 			·····	
					
LUNG (NO. EXAMINED)	(10)	(10)		(10)	· · · · · · · · · · · · · · · · · · ·
Hemorrhage		2			
Pigment Deposition		2	·		
Hyperplasia of Type II Cells		2	·		
Accumulations of Foamy					
Macrophages		2	 		
Peribronchial Lymphoid		·			
Hyperplasia	10	10	<u>:</u>	9	
	:	: 			
BRAIN (NO. EXAMINED)	(10)	(10)			
	! 	: 	: 		
PITUITARY (NO. EXAMINED)	(10)	(10)			·
Cyst	!	1	· .		
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RZ-79 17 Week Sacrifice Male Rats

	Group C	Group H	Group L	Group M	-	
ADRENAL (NO. EXAMINED)	(10)	(9)				
Vacuolated Cortical Cells	5	3				
Hemorrhage				!		
	<u> </u>		· <u></u>	1	·	<u>_</u>
EYE (NO. EXAMINED)	(10)	(10)		 		······································
	<u> </u>			• • • • • • • • • • • • • • • • • • • •		
THYROID (NO. EXAMINED)	(10)	(10)	,			
LABOUR AND EVALUATION	(10)	(10)	·	 		
LARYNX (NO. EXAMINED)	1	. (10)	· · · · · · · · · · · · · · · · · · ·	:		
Hemorrhage Foci of Mononuclear Cells		:	:	······		
FOCT OF MONORACTEAR CELLS		 				
TRACHEA (NO. EXAMINED)	(10)	(10)				
Foci of Mononuclear Cells						
LYMPH NODE, TRACHEOBRONCHIAL			'			;
(NO. EXAMINED)	(9)	(9)				
Hemorrhage	1	ı	:			
Pigment Deposition	2					·
WEART (NO EVANTUER)	: (10)	(10)	<u>;</u>			:
HEART (NO. EXAMINED)	1107	(10)	 -			
Nonsuppurative Myocarditis	5		:	· 		
SPLEEN (NO. EXAMINED)	(10)	(10)		!		
PANCREAS (NO. EXAMINED)	(10)	(10)			<u> </u>	
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₹2-79 17 Week Sacrifice Male Rats

	Group	Group	Group	Group M	
	: C	<u>H</u>	<u> </u>	<u> </u>	
YMPH NODE, POPLITEAL	(10)	(10)	!	:	
NO. EXAMINED)	(10)	(10)			:
Hemorrhage	1	<u> </u>		 	
Pigment Deposition	: 1				
Lymphoid Hyperplasia	1			· ,.	
STOMACH (NO. EXAMINED)	(10)	(10)			
OUODENUM (NO. EXAMINED)	(10)	(10)			
ÇECUM (NO. EXAMINED)	(10)	(10)			
Nematodiasis	1	1		·	
: Hemorrhage		1			
COLON (NO. EXAMINED)	(10)	(10)			
Nematodiasis	3				
Hemorrhage		1	•		
SKIN (NO. EXAMINED)	(10)	(10)			
TESTIS (NO. EXAMINED)	(10)	(10)			
EPIDIDYMIS (NO. EXAMINED)	(10)	(10)	·		
PROSTATE (NO. EXAMINED)	(10)	(10)	·		
JRINARY BLADDER (NO. EXAMINED)	(10)	(10)			
Foci of Mononuclear Cells	·			<u>-</u>	
		1		- 4	

IV-4

RZ-79 17 Week Sacrifice Male Rats						
<u>.</u>	Group C	Group H	Group L	Group M		<u>.</u>
FEMUR (NO. EXAMINED)	(10)	(10)				
		<u>i</u>			:	
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			:	·		
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		IV-5				
E P L Experimental Pathology Labo						

EPL	
	Experimental Pathology Laboratories, Inc.

NZ-79 17 Week Sacrifice Female Rats

	Group C	Group H	Group L	Group M	
NASAL CAVITY-LEVEL I		: 			
NO. EXAMINED)	(10)	(10)	(10)	(10)	
Hemorrhage	4	1	!		
Submucosal Pigment Deposition		2	ı		
Nonsuppurative Rhinitis			1	1	
Hyperplasia of Goblet Cells	1	!	1	. 1 ,	
Cystic Glands				:	
NASAL CAVITY-LEVEL II		!	·	1	
(NO. EXAMINED)	(10)	(10)	(10)	i (10)	
Hemorrhage	3	1			
Submucosal Pigment Deposition	: :	10			
Nonsuppurative Rhinitis					
Foreign Body			 	1	
ASAL CAVITY-LEVEL III			'	•	
(NO. EXAMINED)	(10)	(10)	(10)	(10)	
Hemorrhage	1	1	:		
Submucosal Pigment Deposition		10		4	
Nonsuppurative Rhinitis	<u> </u>	<u>.</u>			
NASAL CAVITY-LEVEL IV	! ! !	1	<u> </u>		
(NO. EXAMINED)	(10)	(10)	(10)	(10)	
Submucosal Pigment Deposition		10		В	
: Hemorrhage	İ				1
Suppurative Exudate					
¥ <u></u>		<u> </u>	·	·	
		<u> </u>		:	
<u> </u>	!				
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IV-6

EPL Experimental Pathology Laboratories, Inc.

RZ-79 17 Week Sacrifice Female Rats

•	Group	Group H	Group Group	
LIVER (NO. EXAMINED)	(10)	(10)	(10)	
Foci of Mononuclear Cells	3	5	4	
Pigment Deposition		10		
Bile Duct Hyperplasia	1	i		
KIDNEY (NO. EXAMINED)	(10)	(10)	(10)	
Pigment Deposition	10	10	10	
Regenerative Tubular			:	
Epithelium		1		
Casts		1	·	
Foci of Mononuclear Cells	2	2	2	
Cyst Tubular Mineralization	10	10	10	
LUNG (NO. EXAMINED)	(10)	(10)	(10)	
Hemorrhage				
Pigment Deposition	·	<u>.</u>	·	
Hyperplasia of Type II Cells		<u> </u>	 	
Accumulations of Foamy			<u>;</u>	
Macrophages		; 		
Peribronchial Lymphoid			,	
Hyperplasia	10	9	9	
BRAIN (NO. EXAMINED)	(10)	(10)		
PITUITARY (NO. EXAMINED)	(10)	(10)		، المحدد من المحدد المحدد المحدد المحدد المحدد المحدد المحدد المحدد المحدد المحدد المحدد المحدد المحدد المحدد
Cyst	!	2		
	<u>!</u>			
		!		

RZ-79 17 Week Sacrifice Female Rats

	Group	Group	Group	Group	1
ADDENIAL (NO EVANTUED)	(10)	(10)	! L	· M	:
ADRENAL (NO. EXAMINED) - Vacuolated Cortical Cells	(10)	(10)	: !	<u> </u>	<u>:</u>
· · · · · · · · · · · · · · · · · · ·		1	i		
1 Hemorrhage		<u> </u>	 		<u>: </u>
EYE (NO. EXAMINED)	(10)	(10)			
THYROID (NO. EXAMINED)	(10)	(8)		· · · · · · · · · · · · · · · · · · ·	:
ARYNX (NO. EXAMINED)	: (10)	(10)	: <u></u>	· 	·
Hemorrhage			!	1	
Foci of Mononuclear Cells		1		i	:
TRACHEA (NO. EXAMINED)	(10)	(10)	<u> </u>	<u> </u>	
Foci of Mononuclear Cel's	1	1	:		
LYMPH NODE, TRACHEOBRONCHIAL	:	`	· · · · · · · · · · · · · · · · · · ·		
(NO. EXAMINED)	(9)	(10)			
Hemorrhage	4	3			·
Pigment Deposition	4	5	:	<u>.</u>	
HEART (NO. EXAMINED)	(10)	(10)	· 	·	
Nonsuppurative Myocarditis	3	3			
SPLEEN (NO. EXAMINED)	(10)	(10)	-		
PANCREAS (NO. EXAMINED)	(10)	(10)			
	:	<u> </u>	· · · · · · · · · · · · · · · · · · ·	· 	<u>:</u>
		1			
[<u>:</u>	·		

RZ-79 17 Week Sacrifice Female Rats

	Group C	Group H	Group L	Group M	i	
LYMPH NODE, POPLITEAL						
(NO. EXAMINED)	(7)	(10)				
Hemorrhage	<u> </u>	<u> </u>	·	<u> </u>	_i	
Pigment Deposition	i				· ·	
Lymphoid Hyperplasia	1		:			
STOMACH (NO EVANINED)	(10)	(10)	·			
STOMACH (NO. EXAMINED)	(10)	(10)			-	
DUODENUM (NO. EXAMINED)	(10)	(10)				
CECUM (NO. EXAMINED)	(10)	(10)		· ·		;
Nematodiasis	!	·	· 		· .	
Hemorrhage						
COLON (NO. EXAMINED)	(10)	(10)			· · · · · · · · · · · · · · · · · · ·	
Nematodiasis	1	<u> </u>			· <u> </u>	!
Hemorrhage	·	: 				<u> </u>
SKIN (NO. EXAMINED)	(10)	(10)	<u> </u>	<u> </u>		
UTERUS (NO. EXAMINED)	(10)	(10)	:			
Dilatation		. 1				
OVARY (NO. EXAMINED)	(10)	(10)	· · · · · · · · · · · · · · · · · · ·			
Parovarian Cyst		1			:	
URINARY BLADDER (NO. EXAMINED)	(10)	(10)	<u></u>			
Foci of Mononuclear Cells	1	<u> </u>	1	<u>-</u>		
		· 	: 	·		

다.RZ-79 나 17 Week Sacrifice Female Rats

-	Greup C	Group H	Group L	Group M	
FEMUR (NO. EXAMINED)	(10)	(10)		· · · · · · · · · · · · · · · · · · ·	·
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IV-10

E P L Experimental Pathology Laboratories, Inc.

H

GROUP	CONCENTRATION
С	Control
L	Low Exposure Concentration
M	Medium Exposure Concentration
Н	High Exposure Concentration

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RZ-79 Group C 17 Week Sacrifice Male Rats 1 3 8 9 X X X X NASAL CAVITY-LEVEL I X 2 2 Hemorrhage 2 Submucosal Pigment Deposition Nonsuppurative Rhinitis Hyperplasia of Goblet Cells Cystic Glands NASAL CAVITY-LEVEL II 2 1 2 Hemorrhage Submucosal Pigment Deposition Nonsuppurative Rhinitis Foreign Body NASAL CAVITY-LEVEL III Hemorrhage Submucosal Pigment Deposition Nonsuppurative Rhinitis NASAL_CAVITY-LEVEL_IV Submucosal Pigment Deposition Hemorrhage Suppurative Exudate [x, <u>x,</u> x, x, x, x, , x, LIVER Foci of Mononuclear Cells Pigment Deposition

V-1

Experimental Pathology Laboratories, Inc.

Bile Duct Hyperplasia

Key P = Present N = No Section
1 = Minima* 2 = Slight
5 = Severe*High 1 = Incomplete Section

A - Autolysis X - Not Remarkable
3 - Moderate 4 - Moderatery Severe

732-79 √37 Week Sacrifice Male Rats						Gr	oup	С				
	A N U I M B A E	3 9 9 8	3 9 9 8	3 9 9 8	3 9 9	3 9 9	3 9 9	3 9 9	3 9 9 8	3 9 9 8	3 9 9 8	
	LR	1 4 0	1 4 1	1 4 2	1 4 3	1 4 4	1 4 5	1 4 6	1 4 7	1 4 8	1 4 9	
KIDNEY												
Pigment Deposition Regenerative Tubular		1	1	1	1.	1_	1	.1.	1	1	1	
<u>Epithelium</u>		1	1		1	1	2	1	1	1	1	
Casts			2									
Foci of Mononuclear Cells			1									
Cyst						···			<u>.</u> .			
Tubular Mineralization		 ∔								<u></u>		
					-	_					.	
UNG		 						-	-		٠	
Hemorrhage						· -·-						
Pigment Deposition			<u> </u>	-		. <u>-</u>			· · ·		-	
Hyperplasia of Type II Cell	<u>s</u>	├ ~-			.	· · -· -						
Accumulations of Foamy		 -									- ·-	
Macrophages												
Peribronchial Lymphoid		ļ										
Hyperplasia	 -	2	_1_	. 1	1	1_	. 1	1,	1	1	. 1	
² BRAIN		X_	. X	. Х	. X	. X	, X	X.	Χ.	Χ.	X	
DITHITADY				 u		 •						
LPITUITARY		X	Χ.	X	. X	, X	. Х	λ		X	Ä,	· · · · · · · · · · · · · · · · · · ·
. Cyst		 		•	•		-					
ADRENAL		1	 X	•	X	X	•		X	X		
Vacuolated Cortical Cells		1	. ^		. ^	^	. 1	1	^	^	1	
N Hemorrhage		1 *	• • •	. •			. •	. •	•	-	•	
Tremor nege		 		-	•					-		

V-2

EPL Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section
1 = Mirima 2 = Slight
5 = Severe High 1 = Incomplete Section

A - Autotya s - X - N - Remarkable 3 - Moderate - 4 - Moderate y Severe High

RZ-79 17 Week Sacrifice Male Rats

Group C

male kats													_
-	A N N U I M M B	3 9 9	3 9 9	3 9 9	3 9 9 8	3 9 9	3 9 9 8	3 9 9 8	3 9 9 8	3 9 9	3 9 9 8	·	
	A E L R	1 4 0	1 4	1 4 2	- 1 4 3	1 4 4	1 4 5	1 4	1 4 7	1 4	1 4 9		
EYE		X	X		X	<u> </u>							
THYROID		X	X	X	X	X	X	X	X	X	X_		
LARYNX		X	X	X	X	<u>X</u>	X	X	X		X		
Hemorrhage Foci of Mononuclear Cells										. <u>2</u> 			
TRACHEA Foci of Mononuclear Cells		X	X	X	X	X	X	X .	X	_ X	X		
LYMPH NODE, TRACHEOBRONCHIAL Hemorrhage		X		X	X	X,	Ŋ		 X	X	X	· · · · · · · · · · · · · · · · · · ·	
Pigment Deposition			1					2					-
HEART Nonsuppurative Myocarditis		1	1	2	X			<u>X</u>	X	X	1		
SPLEEN		X	X	X	 _ X	. x	X	X	X	X	X		-
PANCREAS		X	X_	<u>x</u>	X	X	X	X	X	X	X		
LYMPH NODE, POPLITEAL Hemorrhage		X	X	X	X	X	 X	X	X	X	. 2		
Pigment Deposition Lymphoid Hyperplasia					• ·				- •		1		
L		<u> </u>									_		

Y-3

EPL Experimental Pathology Laboratories, Inc.

P = Present N = No Section
1 = Minima! 2 = Sight
5 = Severe 'High 1 -- Incomplete Section

A = Autolysis 3 = Moderate X = Not Remarkable
4 = Moderately Severe: High

CRZ-79 E17 Week Sacrifice Male Rats	ſ					Gr	onb	C				
	ANUIM BAELR	3 9 8 - 1 4 0	3 9 9 8 - 1 4 1	3 9 8 - 1 4 2	3 9 8 - 1 4 3	3 9 9 8 - 1 4 4	3 9 8 - 1 4 5	3 9 8 - 1 4 6	3 9 9 8 - 1 4 7	3 9 8 - 1 4 8	3 9 8 - 1 4 9	
STOMACH		<u>X</u>	X	X	X	<u>X</u>	X	Ϋ́	X	X	<u>X</u>	
DUODENUM		X_	<u>X</u>	_X_	<u>X</u>	<u>X</u> _	_ X _	_ <u>X</u> _	X	X_	_X_	
CECUM Nematodiasis Hemorrhage		_X	X									
COLON Nematodiasis Hemorrhage		X 	_X			. <u>X</u> _			X.	X.	X	
SKIN		<u></u>	_X_	_ X .	X	X_	X	X.	X .	X	_ X _	·
TESTIS		X_	X_	X	X_	_ X_	. X.	<u>X</u> _	X_	_X_	X_	· ·
EPIDIDYMIS		<u>X</u>	X	_ X _	_X	X _	X .	X	X	X	X	
PROSTATE		X	X	X	X	X	X	X.	X	X	X	
URINARY BLADDER Foci of Mononuclear Cells		X	X.	X.	X	X	X	X	X	X	X	
FEMUR		X	X _	X	X	X_	X	X	X	X	X	
·					V-4	· _	 					

EPL Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section
1 = M-rima: 2 = Slight
5 = Severe High 1 = Incomplete Section

RZ-79 17 Week Sacrifice Group H Male Rats NASAL CAVITY-LEVEL I 1 2 1 1 1 Hemorrhage Submucosal Pigment Deposition Nonsuppurative Rhinitis Hyperplasia of Goblet Cells Cystic Glands NASAL CAVITY-LEVEL II Hemorrhage Submucosal Pigment Deposition Nonsuppurative Rhinitis Foreign Body NASAL CAVITY-LEVEL III Hemorrhage Submucosal Pigment Deposition Nonsuppurative Rhinitis NASAL CAVITY-LEVEL IV Submucosal Pigment Deposition 3 3 3 3 3 3 3 3 3 3 Hemorrhage 1 1 Suppurative Exudate LIVER Foci of Monchuclear Cells 1 1 1 1 1 1 1 1 Pigment Deposition

V-5

E.P.L. Experimental Pathology Laboratories, Inc.

Bile Duct Hyperplasia

Key P = Present

A - Autolysis X - Not Remarkable
3 - Moderate 4 - Moderately Seven

₹₹Z-79 ₹ 7 Week Sacrifice Male Rats	_					Gr	out) H ——				·			·						
	N U M B E R	4 0 0 1 - 1 4 0	4 0 0 1 - 1 4 1	4 0 0 1 - 1 4 2	4 0 0 1 - 1 4 3	4 0 0 1 - 1 4 4	4 0 0 1 - 1 4 5	4 0 0 1 - 1 4 6	4 0 0 1 - 1 4 7	4 0 0 1 - 1 4 8	1 4										
							<u>_¥</u> _			<u> </u>			-	,							
Pigment Deposition Regenerative Tubular		3_	3_	.3	2	2_	2	?_	3	3	3										
Epithelium		2	_2_	. 1_	_1	2	_1	1_	_2_	2	3	<u>-</u>									
Casts		2	2	_1	_1	2	2	1	_2	2	2								. —		
Foci of Mr lear Cells Cyst			_1_			1			1												
Tubular Mineralization								. 											- · · ·		
LUNG	7									- :			-	~							
Hemorrhage		1		1	-				· ·				•							•• · · ·	
. Pigment Deposition	1																				
Hyperplasia of Type II Cells	- 1		1_		· ·-			•			.								 .		
Accumulations of Foamy															_			-			
Macrophages Peribronchial Lymphoid															•				-	-	
Hyperplasia	_	1_	2			1									-	· •			-	•	
3RAIN		<u>X</u>	Χ.	χ	X	X	X	X	X	X	. X	-			. •		•				
PITUITARY		<u>X</u>	X	X	 . X	 X		 . X	- . X	X	- , X					-					-
Cyst	\dashv					-	. P	-		• .	-	•					-		-		
ADRENAL			X	N	X	X	-	X	_ X	_ X						-					
Vacuolated Cortical Cells Hemorrhage		1_			-		. 1		-		. 1					-					

V-6

Experimental Pathology Laboratories, Inc.

P - Present N - No Section
1 - Minimal 2 - Slight
5 - Severe High I - Incomplete Section

RZ-79 17 Week Sacrifice Group H Male Rats EYE THYROID **X X X X X X X X X** LARYNX Hemorrhage Foci of Mononuclear Cells TRACHEA \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} Foci of Mononuclear Cells LYMPH NODE, TRACHEOBRONCHIAL Hemorrhage Pigment Deposition **HEART** Nonsuppurative Myocarditis SPLEEN X = X = X = X = X = X = X = X = X**PANCREAS** LYMPH NODE, POPLITEAL Hemorrhage

v		۰
¥	•	1

E P L Experimental Pathology Laboratories, Inc.

Pigment Deposition
Lymphoid Hyperplasia

Key P-Present

N= No Section
2 = Slight
1 = Incomplete Section

A = Autorysis X = Not Remarkable
3 = Mode-ale 4 = Moderale's Severe Hi

デRZ-79 ど17 Week Sacrifice Male Rats

Group H

Male Rats												
- -	A N U I MI M B A E L R	4 0 0 1 - 1 4 0	4 0 0 1 - 1 4 1	4 0 0 1 - 1 4 2	4 0 0 1 - 1 4 3	4 0 0 1 - 1 4 4	4 0 0 1 - 1 4 5	4 0 0 1 - 1 4 6	4 0 0 1 - 1 4 7	4 0 0 1 - 1 4 8	4 0 0 1 - 1 4 9	
STOMACH		X	X	X	X	X	X	X	X	_X	X	
DUODENUM		X	X	X	X	X	X	X_	<u>X</u>	X	X	
CECUM		X	X	X	X	_	<u> X</u>	X	_X_	X		
Nematodiasis Hemorrhage										·	1.	
COLON Nematodiasis							X		_X			
Hemorrhage										.		
SKIN		_X_	<u>X</u>	X	<u>X</u>	X	<u>X</u>	. X	X	X	X	
TESTIS			_X_	<u>X</u>	X	X	, X	X	X	X	X_	
EPIDIDYMIS		X_	<u>X</u>	X	X	_ X	X	X.	X	X	X .	
PROSTATE		Χ.	_ X _	X	X	X	X	X	X	X	X	. <u> </u>
URINARY BLADDER		X	X	X	X	X	X	X	X	X	X	
FEMUR		X	X	X	X	X	X	X	X	X	X	
					•		•					· · · · · · · · · · · · · · · · · · ·
		<u> </u>										

V-8

EPL Experimental Pathology Laboratories, Inc.

P = Pinsent N = No Section
1 = Minima: 2 = Slight
5 = Severe/High I = Incomplete Section

RZ-79 17 Week Sacrifice Male Rats		_			Gr	oup	L													1
A N N U 1 M M B A E L R	9 9	3 9 9 - 1 4	3 9 9 - 1 4 2	3 9 9 - 1 4 3	3 9 9 - 1 4 4	3 9 9 - 1 4 5	3 9 9 - 1 4 6	3 9 9 - 1 4 7	3 9 9 - 1 4 8	3 9 9 - 1 4 9										
NASAL CAVITY-LEVEL I		X	X	Ť				X												J.,
Hemorrhage	1										<u></u> .									
Submucosal Pigment Deposition	\bot											_ _	, -				 -			
Nonsuppurative Rhinitis	+				· - 			_								- -				
Hyperplasia of Goblet Cells	 	-		<u>-</u> .		· -								 -		- -				١,,
Cystic Glands	 																			12
NASAL CAVITY-LEVEL II	X	X	X	X	X	X	X	X	X	X										
Hemorrhage									- 			_								
Submucosal Pigment Deposition	_		.								-			· - -		_ _ -				┨::
Nonsuppurative Rhinitis		-									-									
Foreign Body			.	. .									-				-	-		 }
NASAL CAVITY-LEVEL III	X	X	X	X	 X	- X		X	X	X					. <u>.</u>					1.3
Hemorrhage				<u>. </u>		<u> </u>	1										•		- -	
Submucosal Pigment Deposition													_		<u></u>					``
Nonsuppurative Rhinitis				.							-		-			-		· - •		1:
		<u>۔</u>							. ,						-		-			1
NASAL CAVITY-LEVEL IV	- 1	X	. X	. X	X	X	X	X	X	. X .			-							-
Submucosal Pigment Deposition			• -					. - ·	. -	. .	•	•	•	•	-			-		
Hemorrhage Evudata					•	-		-			٠	٠	-	٠	÷			-		:
Suppurative Exudate			• -	•	•	-			•	• .	-	-			•			•	•	-
	1-		•	-	•	-		-	•			•	-	-	-				•].
		- -						_	•			_		•				•	-]:
				- -				<u>.</u> .				-					ē			
	•																			

EPL Experimental Pathology Laboratories, Inc.

P + Present N + No Section
1 + Minimal 2 + Slight
5 + Severe'High I + Incomplete Section

MAZ-79 27 Week Sacrifice Male Rats					Gr	oup	M												
A N U I M B A E L R	4 0 0 0 - 1 4 0	4 0 0 0 1 4	4 0 0 0 1 4 2	4 0 0 0 - 1 4 3	4 0 0 0 - 1 4 4	4 0 0 0 1 4 5	1 4	1 4	1 4	4 0 0 0 - 1 4 9				-					
HASAL CAVITY-LEVEL I		X	X		X				X										
Hemorrhage						2					. 								
- Submucosal Pigment Deposition]												·						
Nonsuppurative Rhinitis							1												
Hyperplasia of Goblet Cells	1					.										_			
Cystic Glands	-			1_				1						~	· ·				
HASAL CAVITY-LEVEL II	X	<u> </u>	X		<u>X</u> .		X				·								
Hemorrhage	ļ			_1		1									• • •				-
Submucosal Pigment Deposition	<u> </u>								. –								_		
Nonsuppurative Rhinitis	J			_1					1	. .		· ·			<u> </u>	_	-		
- Foreign Body	┇			.								_							
	J										. <u> </u>	<u>.</u>			•			. .	
NASAL CAVITY-LEVEL III	J	_X	<u> X</u>	X		_X_	X	_ X _	X	<u>X</u> _									
Hemorrhage	<u> </u>												_						
Submucosal Pigment Deposition	1				1.	_									-				
Nonsuppurative Rhinitis	<u> </u>					_				-			-				-		
<u> </u>	┧_		.						_										
TASAL CAVITY-LEVEL IV	ļ <u>.</u>	.	Χ.	X			X.												
Submucosal Pigment Deposition	1.	_1_		- - -	. 1.	1		2	1	1_									-
. Hem <u>orrhage</u>	ļ	• · · -		- .															
Suppurative Exudate	-																		
				V			 V	¥	. y	 ¥									
Foci of Mononuclear Cells	† ^	_ ^.			1	^	^.	. ^										•	
T. Diames Branchine	1-	•··-·	•	•	•														
Bile Duct Hyperplasia											-	-		-	•		•	- •	-
Dite Duct Hyperplasia	٠																		

V-10

EPL Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section
1 = M (ima) 2 = Slight
5 = Severe High 1 = Incomplete Section

RZ-79 17 Week Sacrifice Male Rats					Gr	oup	M					_ [
A N N U I M M B A E L R	4 0 0 0 - 1 4 0	4 0 0 0 - 1 4 1	4 0 0 0 - 1 4 2	4 0 0 0 - 1 4 3	4 0 0 0 - 1 4 4	4 0 0 0 1 4 5	4000	4 0 0 0 - 1 4 7	0000-148	4 0 0 0 1 4	- 1 4	
KIDNEY	<u> </u>							.	. -			_ {
Pigment Deposition	1_1_	1	. 1	1	1	2_	_1	_1_	1	1	<u> 1 </u>	_ !
Regenerative Tubular	<u> </u>											_
Epithelium	<u> </u>	1	1			1	1	_1_	2	_ 1	1	
Casts	1		1_	_1	1_	1_	1	_ 2	<u> </u>	1	1	4.
Foci of Mononuclear Cells	1			1		1	1.	_1_		1	1	_ ;
Cyst	<u> </u>				-					. – -		4
Tubular Mineralization	ļ 											;
	ļ		<u>.</u>							_		-
LUNG		<u> </u>	– .				-				<u> </u>	-1:
Hemorrhage	-								-			1
Pigment Deposition	\			-		-		-		-		
Hyperplasia of Type II Cells	↓		_	-	-	-						
Accumulations of Foamy		_	- · -	-		·			. .			
Macrophages	ļ			-			-					
Peribronchial Lymphoid	- l	-						-		- - -	-	
Hyperplasia	1		. 2	. 1	1	_ 1	. 1	_ 1	1		1	
	_					-		-				
	-	-	-	-	-	÷		÷				}
		-		-							and the second s	-
		-				-						
	-	-		-		-		-				-
	· · · -	-	•	-	•						and the second second second second second	
		-		. –				-				
	 	-		•	٠							1
				- .				•				
										-		

GROUP	CONCENTRATION
C	Control
L	Low Exposure Concentration
М	Medium Exposure Concentration
Н	High Exposure Concentration

3

#\$6 \$50 \$50 \$5**4**

M

RZ-79 17 Week Sacrifice Female Rats	Group C	
- A N N U I M M B A E L R		
NASAL CAY) TY-LEVEL I	x x x x x	
Hemorrhage	2 1 2 1	
Submucosal Pigment Deposition		
Nonsuppurative Rhinitis		
Hyperplasia of Goblet Cells	11	
Cystic Glands		-
NASAL CAVITY-LEVEL II		
Hemorrhage	2 1	ŀ
Submucosal_Pigment_Deposition Nonsuppurative_Rhinitis		
Foreign Body		1 1
NASAL CAVITY-LEVEL III Hemorrhage	<u> </u>	
Submucosal Pigment Deposition Nonsuppurative Rhinitis		
NASAL <u>CAVITY-LEVEL IV</u> _Submucosal <u>Pigment Deposition</u>	1	
Hemorrhage		
Suppurative_Exudate		
LIYER	x x x x x x	
Foci of Mononuclear Cells	1 1 1	
Pigment Deposition		
Bile Duct Hyperplasia		

V-12

EPL Experimental Pathology Laboratories, Inc.

A = Not Remarkable 4 = Moderately Severe High A = Autolysis 3 = Moderate

.RZ-79 ₹17 Week Sacrifice ₹Female Rats		····				Gr	oup	С				
	A N N U I M M B A E L R	3 9 9 8 -6 4 0	3 9 9 8 - 6 4 1	3 9 9 8 - 6 4 2	3 9 9 8 6 4 3	3 9 8 - 6 4 4	3 9 9 8 - 6 4 5		-	3 9 9 8 6 4 8	3 9 8 - 6 4 9	
KIDNEY												
Pigment Deposition Regenerative Tubular Epithelium Casts		1	1	1_	1	1_	1	1	1	1	1	
, ,		-										
Foci of Mononuclear Cells		 -					_1_			1_		
Cyst Tubular Mineralization		1	_2	2	2	1	1	2	2	3_	3	
LUNG									•-	•		
Hemorrhage												
Pigment Deposition	• • • • • • • • • • • • • • • • • • • •								-			
Hyperplasia of Type II Cells	 S								•			
Accumulations of Foamy				-		-					• • • •	
Macrophages		 -							-			
Peribronchial Lymphoid										•		
Hyperplasia		1	i	1	1	1	1	1	1	1	1	
BRAIN	- ·-·	X	X	X	X	X	X	X	X	X	X	· · · · · · · · · · · · · · · · · · ·
P1TUITARY		<u>x</u>	X	X	X	X	 X	X	X	 X		
Cyst												
					.						_	
ADRENAL		X	X.	X	X	X	X	X	X	X	X	
Vacuolated Cortical Cells]					•					
Hemorrhage										_		
L <u>.</u>		<u></u>										
<u>.</u>												

V-13

EPL Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section
1 = Minima: 2 = Slight
5 = Severe High 1 = Incomplete Section

RZ-79 17 Week Sacrifice Female Rats					Gr	oup	С					
A N U I M M B A E L R	9	3 9 8 - 6 4 1	3 9 9 8 - 6 4 2	3 9 8 - 6 4 3	3 9 8 - 6 4	3 9 8 - 6 4 5	3 9 9 8 - 6 4 6	3 9 9 8 - 6 4 7	3 9 9 8 - 6 4 8	3 9 9 8 - 6 4 9		
EYE	X	X	_X	X	X	X	X	X	X	X		
THYROID	X	X	X	X	X	X	X	X	X			
LARYNX Hemorrhage Foci of Mononuclear Cells					- <u>-</u> -			·		X		
TRACHEA Foci of Mononuclear Cells			. 1	_ X_	_X	X	X	. X	. X	. X		
LYMPH NODE, TRACHEOBRONCHIAL Hemorrhage Pigment Deposition		_ X	_1_	_ X	N_ 	2	1.1.	. X .	X	1 2		1
HEART Nonsuppurative Myocarditis	1				_X_		X	X		_		
SPLEEN	X	_ X	X	X	X	X	X	. X	X		·	
PANCREAS	x	_ X	. X	<u> </u>	_ X	. X	. X	X	. X			
LYMPH NODE, POPLITEAL Hemorrhage Pigment Deposition Lymphoid Hyperplasia	_ -			-		- 		<u>.</u>	-			

V-14

EPL Experimental Pathology Laboratories, Inc.

P - Present N - No Section

1 - Minma 2 - Slight

5 - Severe High I - Incomplete Section

A = Autorysis | X = Nut Femalikable | 3 = Moderate | 4 = titracrutely Severe Migr

RZ-79 17 Week Sacrifice Female Rats						Gr	oup	C					·			
	A N N U I M M B A E L R	3 9 9 8 -6 4 0	3 9 8 - 6 4	3 9 9 8 - 6 4 2	3 9 9 8 - 6 4 3	3 9 9 8 - 6 4	3 9 9 8 - 6 4 5	3 9 9 8 - 6 4 6	3 9 9 8 - 6 4 7		3 9 8 - 6 4 9					
STOMACH		X	X	_X	X	X	X	X	X	X	X					
DUODENUM		X	X	X	X		X	X	X	<u>X</u>	X	·				
CECUM		X	X	X	X	λ	X	X	X	X	X				 .	
Nematodiasis																
Hemorrhage						·-· -										* ****
COLON			X	Χ	X	X	X	X	X	X	X					- .
- Nematodiasis		Р														
Hemorrhage				-											· ·-	÷
SKIN		X	X	X	X	X	X	X	X	X	X					
UTERUS		X	X	X	X	X	X	 X	X	X	X	- ·-			•	•
Dilatation						-	-									
OVARY		X	X_	X	 . X	X	X _	X	_X	X	X				-	
Parovarian Cyst			• ·													
URINARY BLADDER		X	X	X	X		X	X	X	X	X			4		*
Foci of Mononuclear Cells		ļ				1				. ,		,				

V-15

EPL Experimental Pathology Laboratories, Inc.

FEMUR

(ay P = Present 1 = Minima!

N = No Section
2 = Sight
1 = Incomplete Sect

A - Autotysis X - Not Remarkable
3 - Moderate 4 - Moderately Severe High

RZ-79 17 Week Sacrifice Female Rats	_					Gr	oup	Н					
N 1 1	U M B E	4 0 1 5 4	4 0 0 1 - 6 4 1	4 0 0 1 -6 4 2	4 0 0 1 - 6 4 3	4 0 0 1 - 6 4 4	4 0 0 1 -6 4 5	4 0 0 1 - 6 4 6	4 0 0 1 - 6 4 7	4 0 0 1 - 6 4 8	4 0 0 1 - 6 4 9		
NASAL CAVITY-LEVEL I	_	<u>X</u>	X			<u>X</u> _	.X .	X	_ X	_ X	- -		
Hemorrhage				1						_ -		•	
Submucosal Pigment Deposition	-				1						1	· — ~ — — — — — — — — — — — — — — — — —	
Nonsuppurative Rhinitis	_						-						
Hyperplasia of Goblet Cells							. .			· · · · 			
Cystic Glands					·					· · · · - ·			
NASAL CAVITY-LEVEL II						·							
Hemorrhage	-			_1_									
Submucosal Pigment Deposition		2	2	_2 _	2	. 1	2	1	2	2	_ 2		
Nonsuppurative Rhinitis												·	
Foreign Body	_										•-		
NASAL CAVITY-LEVEL III								•		· ··			
Hemorrhage	_			_1_	. —								
<u>Submucosal Pigment Deposition</u>		3_	3_	2	3	2	. 2	2	3	. 2	_2		
Nonsuppurative Rhamitis					-		-		-				
NASAL CAVITY-LEVEL IV						_					-		
Subm <u>ucosal Pig</u> ment Deposition Hemorrhage		3_	3 .	3	3					. 3	3		. ,
Suppurative Exudate	_						•						
LIYER	- 1												
Foci of Mononuclear Cells									. 1		. 1		
Pigment_Deposition		1.	1.	1	. 1	. 1	. 1	1	. 1	1	. 1		
Bile Duct Hyperplasia				_									

V-16

E P L Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section
1 = Minimal 2 = Sight
5 = Severe High 1 = Incomplete Section

≒RZ-79 ₹-17 Week Sacrifice Female Rats						Gr	oup	н			
	A N M M M B A E	4 0 0 1	4 0 0 1	4 0 0 1	4 0 0 1	1	4 0 0 1	4 0 0 1	4 0 0 1	4 0 0 1	4 0 0 1
8	L R	6 4 0	6 4 1	6 4 2	6 4 3	6 4 4	6 4 5	6 4 6	6 4 7	6 4 8	6 4 9
KIDNEY											
Pigment Deposition		3	3	3	2	2	3	3	3	3	3
Regenerative Tubular											
<u>Epithelium</u>							1				
Casts		1_									
Foci of Mononuclear Cells				1					1_		
Cyst											
Tubular Mineralization		2	2_	2	2	2	2_	3_	2_	2	2
LUNG					X						
Hemorrhage											
Pigment Deposition											
Hyperplasia of Type II Cells											
Accumulations of Foamy									_		
Macrophages											
Peribronchial Lymphoid											
Hyperplasia		1	1	1		1	1	1	1	1	1
BRAIN		 X_	X.	X	X	X	X	X	. X	X.	X
PITUITARY		Ϋ́			X	X _	Х.	Χ.	X		· *
^ Cyst			<u>P</u>							Ρ.	
ADRENAL		·			·	. X	V	Y	¥	Y	
Vacuolated Cortical Cells	· · -	^.	. <u>^</u> .		. ^	. ^ .	. ^ .	^	^ .	^ .	• • • • • • • • • • • • • • • • • • • •
Hemorrhage	·-·· —-			2							
Tiemor triage				- _							

V-17

EPL Experimental Pathology Laboratories, Inc.

Key Present N=No Section
1 ~ Minimal 2 ~ Sight
5 ~ Severe*High | 1 ~ Incomplete Section

A = Autolysis X = Not Remarkable 3 = Moderate 4 = Muderately Severe High

RZ-79 17 Week Sacrifice Female Rats	i		-			Gr	oup	Н									 		
•	A N U I M B A E L R	4 0 0 1 - 6 4 0	4 0 0 1 - 6 4 1	4 0 0 1 - 6 4 2	4 0 0 1 - 6 4 3	4 0 0 1 - 6 4 4	4 0 0 1 - 6 4 5		_	4 0 0 1 - 6 4 8	4 0 0 1 - 6 4 9								
EYE		X	X	_X	X	X	_X_	X	X	X		_							
THYROID		N	X	N	X	X	Χ_	X	X	X	<u>X</u>				-		 		
LARYNX Hemorrhage Foci of Mononuclear Cells		_			. 						X		 -				 	·	
TRACHEA Foci of Mononuclear Cells		-						. <u>X</u>	. 1	<u>X</u>	. X						 		_
LYMPH NOOL, IRACHEOBRONCHIAL Hemorrhage						X	_ X	X		<u> </u>	. X		. .	. -	. .		 · -	. <u>.</u>	
Pigment Deposition									1.	<u></u>		 - · ·				- -	 		
MEARINonsuppurative Myocarditis		1				X	X	X		_ X_	. X	- -						 - -	
SPLEEN		X	X	X	. X	X	X	X	X	X	X	•			•				
PANCREAS		X	. X	X	, X	X	_ X	. X	X	X	X	-						٠	
LYMPH NODE, POPLITEAL Hemorrhage Pigment Providion Lymphoid proviplasia	-	X	 , X	X	. X	X	X	X	X	X	X		•						

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Experimental Pathology Labora es in:

eyer) NH No Section

-RZ-79 17 Week Sacrifice Group H Female Rats 0 0 6 8 STOMACH DUODENUM x x x x x x x x x x x **CECUM** Nematodiasis Hemorrhage COLON P_____ Nematodiasis Hemorrhage SKIN UTEPUS Dilatation x x x x x x x x x x Parovarian Cyst x x x x x x x x x x URINARY BLADDER Foci of Mononuclear Cells FEMUR

V-19

EPL Experimental Pathology Enboratories, Inc.

Key P = Frequent
1 = Minima:
5 = Severe the

N= No Section
7 = 5 grit
1 = Incomplete Section

A = A 21 yes 3 = First Remarkation 3 = Moderate 4 = Moderate y Stockher mgt

RZ-79 17 Week Sacrifice Female Rats			<u> </u>			Gr	oup	L 					 						_
•	ANUIM BAELR	3 9 9 - 6 4 0	3 9 9 - 6 4	3 9 9 - 6 4 2	3 9 9 - 6 4 3	3 9 9 - 6 4	3 9 9 - 6 4 5	3 9 9 - 6 4 6	3 9 9 - 6 4 7	3 9 9 - 6 4 8	3 9 9 - 6 4 9								
NASAL CAVITY-LEVEL I		_X	_X_	X	X_	X	_X	<u>X</u>	Ţ	_X_			 						
Hemorrhage		ļ				-		 -	· -				 -		_	· _			4
Submucosal Pigment Deposition	ın	ļ		·						 -			 			·-· -			
Nonsuppurative Rhinitis	!						_						 						\dashv
Hyperplasia of Goblet Cells		 													-				\dashv
Cystic Glands	!																		
NASAL CAVITY-LEVEL II Hemorrhage		1				. X .	<u> </u>	Χ.	X.	_ X	<u>_X</u>		 						ı
Submucosal Pigment Deposition	วท	1																	
Nonsuppurative Rhinitis		1												-	-		-		
Foreign Body		ļ							-	-					-	-	•		
NASAL CAVITY-LEVEL III Hemorrhage		1												<u> </u>			-		-
Submucosal Pigment Deposition		i												-	-				
Nonsuppurative Rhinitis					•									÷		•			
NASAL CAVITY-LEYEL IYSubmucosal Pigment Deposition		X	X.	. X		. X .	X	X	X,	. X .	. X .	. <u>-</u>		-					
Hemorrhage	-		<u>.</u>				-						-	-					
Suppurative Exudate				.								-	•						
				-			-					-							
]								-			-						
		┨					-					-						•	

V-20

77-79 7 Week Sacrifice Female Rats	1	·	· · · · · ·			Gr	oup	M									 	
8	N N N N N N N N N N N N N N N N N N N	4000 - 640	4 0 0 0 - 6 4 1	4 0 0 0 - 6 4 2	4 0 0 0 - 6 4 3	4 0 0 0 - 6 4 4	4 0 0 0 - 6 4 5	4000-646	4 0 0 0 - 6 4 7		4 0 0 0 - 6 4 9							
-ASAL CAVITY-LEVEL I		X	X	X		X	X		X	X	X							
Hemorrhage																		
Submucosal Pigment Deposition	n													· ·				
Nonsuppurative Rhinitis					1													
Hyperplasia of Goblet Cells								1								 	 	
Cystic Glands																 	 	
				-														
ASAL CAVITY-LEVEL II		X	_X_	_X_	X	X		X	<u> X</u>	X	_X .					 	 	
Hemorrhage					·				-		_				~	 	 	
Submucosal Pigment Depositio	n															 	 	
Nonsuppurative Rhinitis							· · -									 	 	
- Foreign Body							P						_			 	 	
			 _		•		~							•	_	 	 	 · · · — -
NASAL CAVITY-LEVEL III		X	_X_		X	X		-	X		_ X					 		
Hemorrhage					•				·- <u>-</u> .					.				
Submucosal Pigment Depositio	n			1			1	1		1				.		 _	 _	
Nonsuppurative Rhinitis										_								 . .
·.										<u>.</u> .		_		_		 _		
ASAL CAVITY-LEVEL IV		X_		. <u>-</u> -				1										
Submucosal Pigment Depositio	n_		1	1	1	1	1		1	1	1			_			_	
Hemorrhage										_			-					
Suppurative Exudate										_					_			
			· •		,								•					
IVER		X	X	X	,	X		X	X									
Fuct of Mononuclear Cells					1		1			1	. 1		-					
k :		1												-				

V-21

J. P.L Experimental Pathology Laboratories, Inc.

Pigment Deposition

Bile Duct Hyperplacia

Yey P Present N ~ Nc Section
1 = Minimal 2 + 5-ght
5 = Severe High 1 + Incomplete Section

A = Autorysis X = for Fig. areable 3 = Writingto 4 = M of ale i Severe High

RZ-79 17 Week Sacrifice Female Rats		_			Gr	oup	M													
A N U I M M B A E L R	4 0 0 0 - 6 4 0	4 0 0 0 - 6 4 1	4 0 0 0 - 6 4 2	4000-643	4 0 0 0 - 6 4 4	4 0 0 0 - 6 4 5	4 0 0 0 - 6 4 6	4 0 0 0 - 6 4 7	4000 - 648	4000-649										
KIDNEY																				
Pigment Deposition Regenerative Tubular Epithelium Casts	1						. —													2.5
Foci of Mononuclear Cells	\dagger			1			<u> </u>		-					• •						
Cyst				- 📤 -																-
	2	2	2	2	2_	1	2	3	1	3				- .						133
LUNG	 		X	· · · ·		· · ·				·	<u>-</u>	 				<u>-</u>				, (4)
Hemorrhage	7			· . •									· · · ·		•					=
Pigment Deposition													•		•		•		• •	
Hyperplasia of Type II Cells Accumulations of Feamy	1										. - -						- -		<u>.</u>	
<u>Macrophages</u>	í							-						-			. .	•	-	
Peribronchial Lymphoid Hyperplasia	ſ	 1		 1				 1	1		·								.	1
	1 -	-	- •·	• <i>.</i>	. •	•	· •••	. •		· -										/
										<u>.</u>		•								_
	-	-	- ·							-		-	Ē	-						
] _		-							-				ė						
			<u>.</u> .																	
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	1			•		•				-		•	•	•						

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES

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RZ-79 17 Week Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

H - Sacrificed

Group Number

Males

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Species

Dosage Level: High Exposure

Accumulations of foamy macrophages; pigment deposition; hyperplasia of type II cells Hemorrhage; accumulations of foamy macrophages; pigment deposition; hyperplasia of type II cells Microscopic Observations No corresponding leston No corresponding leston No corresponding lesion No corresponding lesion No corresponding lesion No_corresponding_leston No_corresponding_lesion No corresponding leston Dull pink, diffuse brown/yellow Client's Gross Observations Diffuse_yellow/brown Diffuse yellow/brown Diffuse_yellow/brown Client's Tissue Identification 4001-145 Lung 4001-146 Lung 4001-147 Lung 4001-148 Lung 4001-143 Lung 4001-144 Lung 4001-149 Lung 4001-142 Lung 4001-140 Lung 4001-141 Lung Rats Animal Number

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| 1998年 | 東京 | 1998年 | 1999年

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	Sacrifice
62-7	
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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

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Anmal	Client's Tissue Identification	Client's Gross Observations	Microscopic Observations
4000-142		Dull pink throughout	No corresponding lesion
 			
†			
 			
 -			
·			
1			
 - 			

RZ-79 17 Week Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Chemis Tissue identification Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal	Species Rats	ts Sex Females	Group Number H - Sacrificed	Dosage Level: High Exposure	
Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Yellow Yellow Pigment, yellow, minimal Yellow Yellow Yellow Pigment, yellow, minimal Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow	Anmal	Client's Tissue Identification	Clierd's Gross Observations	Microscopic Observations	ļ
Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal	4001-640	┿	Yellow	No corresponding leston	1
Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Yellow Yellow Yellow Yellow Yellow Pigment, yellow, minimal Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow Yellow		Lung	Pigment, yellow, minimal	No_corresponding lesion	- 1
Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Yellow Yellow Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal		Ovary	Bilateral cysts	No_corresponding_leston	1
rellow rellow, minimal rellow pigment, yellow, minimal rellow rellow pigment, minimal rellow rellow pigment, minimal rellow pigment, yellow pigment, yellow rellow	4001-641		Yellow	No corresponding leston	
Pigment, yellow, minimal Yellow Yellow Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Yellow Pigment, yellow, minimal Yellow		Lung	Pigment, yellow, minimal	No corresponding leston	1
Pigment, yellow, minimal Yellow Yellow Yellow Pigment, yellow, minimal Yellow Pigment, yellow Yellow Yellow Yellow Yellow Yellow	4001-642	Skin	Yellow	No corresponding leston	- [
Yellow pigment, minimal Yellow Pigment, minimal Yellow Pigment, yellow, minimal Yellow Yellow Yellow Yellow		Lung	Pigment, yellow, minimal	No corresponding leston	
reobronchial lymph node Reddened, enlarged Yellow pigment, minimal Yellow Pigment, yellow, minimal Yellow Yellow Yellow	4001-643	Skin	Yellow	No corresponding leston	- 1
Yellow Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow Yellow		Tracheobronchial lymph node	Reddened, enlarged	Hemorrhage; pigment deposition	- 1
Yellow Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow		Lung	Yellow_pigment, minimal	No corresponding leston	
Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow	4001-544	Skin	Yellow	No corresponding leston	
Pigment, yellow, minimal Yellow Pigment, yellow, minimal Yellow	4001-645	Skin	Yellow	No corresponding leston	1
Pigment, yellow, minimal Yellow		Lung	Pigment, yellow, minimal	No corresponding lesion	l l
Pigment, yellow, minimal Yellow Yellow nigment, minimal	4001-646	Skin	Yellow	No corresponding leston	- 1
Yellow Yellow		Lung	Pigment, yellow, minimal	No corresponding leston	- 1
(Vellow nioment, minimal	4001-647	Skin	Yellow	No corresponding leston	
		Lung	Yellow pigment, minimal	No corresponding lesion	- [

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RZ-79 17 Week Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species Rats

Sex Females

Group Number: H - Sacrificed

Dosage Level: High Exposure

Animal Number	Chent's Tissue Identification	Cliert's Gross Observations	Microscopic Observations
4001-647 (Cont'd)	Ovary	Left cystic	Parovarian cyst
4001-648	Skin	Yellow	No corresponding lesion
	Lung	Minimal yellow pigment	No corresponding leston
4001-649	Skin	Yellow	No corresponding lesion
	Lung	Minimal yellow pigment	No corresponding leston
			•
			-

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APPENDIX II

EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

LOYELACE INHALATION TOXICOLOGY RESEARCH INSTITUTE

90 DAY REPEATED INHALATION EXPOSURES OF RATS TO SOLVENT YELLOW-GREEN DYE MIXTURE

PATHOLOGY REPORT

Submitted to:

Lovelace Inhalation Toxicology Research Institute Alburquerque, New Mexico 87185

August 13, 1985

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EXPERIMENTAL PATHOLOGY LABORATORIES, INC.

10 DAY REPEATED INHALATION EXPOSURES OF RATS TO SOLVENT YELLOW-GREEN DYE MIXTURE

PATHOLOGY SUMMARY

A histopathologic evaluation of selected tissues from male and female rats exposed to Solvent Yellow-Green Dye Mixture was conducted to provide information on the inhalation toxicity of dyes present in colored smoke munitions. The experimental design for this study was as follows:

Group	Treatment	Dose* (mg/m3)	90 (per of Day Ifice	_30	als Day overy
			M	F	<u> </u>	王
L	Controls	0	10	10	10	9**
M	Low Exposure Concentration	1	10	10	10	10
N	Medium Exposure Concentration	10	10	10	10	10
0	High Exposure Concentration	100	10	10	10	10

^{*}Rats were exposed six hours/day, five days/week for thirteen weeks. **One animal escaped.

According to protocol, routine hematoxylin and eosin stained slides from the following tissues were prepared for all animals: skin, tracheobronchial lymph node, popliteal lymph node, spleen, femur, larynx, nasal cavity (four levels), trachea, lung (four lobes), heart, stomach, duodenum, cecum, colon, liver, pancreas, kidneys, urinary bladder, epididymis, testis, prostate, uterus, ovary, adrenal, thyroid, brain, pituitary, eyes, and any gross lesions. Microscopic evaluation was performed on all of the listed tissues from the control and high

PATHOLOGY SUMMARY

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a no-effect level for each tissue having a treatment-related effect.

In general, the tissues called for to be examined by protocol are represented in the Histopathology Incidence Tables. Only a few tissues were inadvertently missed at the time of necropsy or lost during histologic processing. In some instances, the posterior portion of the nasal cavity had been damaged and complete sections of four levels of the nasal cavity could not be obtained.

Microscopic findings for each tissue examined from each animal are listed in the Histopathology Incidence Tables. All lesions are summarized by treatment groups in the Summary Incidence Tables together with the total number of animals in each group for which the tissues were examined. A tabulation of gross lesions observed at the time of necropsy with the corresponding microscopic change, if appropriate, is given in the Correlation of Gross and Microscopic Findings Tables. The descriptions of gross findings on these tables were transcribed from the Individual Animal Necropsy Sheets prepared at the time the necropsies were performed.

RESULTS

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Ninety-Day Exposure

Inhalation of Solvent Yellow-Green Dye Mixture at 100 mg/m³ six hours/day, five days/week for thirteen weeks resulted in changes in the lungs, nasal cavity, tracheobronchial lymph node, kidneys, and liver. In the lungs, slight to moderate accumulations of foamy

appearing alveolar macrophages containing minimal to slight amounts of pigment were noted in the alveoli adjacent to the respiratory bronchioles in all high dose rats. These accumulations of alveolar macrophages were accompanied by slight to moderate hyperplasia of Type II cells (granular pneumocytes). In the nasal cavity, submucosal pigment deposition was noted at most levels in nearly all high dose rats. The pigment deposition was heaviest at Level III and Level IV. In the tracheobronchial lymph node, hyperplasia of foamy macrophages (reticuloendothelial cells) with minimal pigment deposition and slight to moderately severe lymphoid hyperplasia were present. In the kidneys, an increase in granular pigment present in the cortical tubules was noted in all high dose rats. In the liver, minimal granules of pigment were noted in the bile duct epithelium or hepatocytes adjacent to the bile ducts in all high dose rats.

In the rats exposed to Solvent Yellow-Green Dye Mixture at 10 mg/m^3 , only lung, nasal cavity, tracheobronchial lymph node, liver, and kidneys were examined. Minimal lung lesions similar to those noted in the high dose rats occurred in three males and three females. The lesions were single lesions and tended to be at the margins of the lung lobes. In the nasal cavity, minimal submucosal pigment was noted at Level III in one male and four females, and at Level IV in two females. In tracheobronchial lymph nodes, hyperplasia of foamy macrophages with minimal pigment deposition was noted in two males and two females. Lymphoid hyperplasia was noted in an additional male.

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Pigment deposition in the kidneys was comparable to the controls. In the liver, minimal granules of pigment were noted in two females.

In the rats exposed to Solvent Yellow-Green Dye Mixture at 1 mg/m³, the lung and nasal cavity were examined from both sexes; the liver was also examined from the females. No compound-related histomorphologic alterations were noted in any of these tissues.

Thirty-Day Recovery

Inhalation of Solvent Yellow-Green Dye Mixture at 100 mg/m³ for ninety days followed by a thirty-day recovery period resulted in lung lesions similar to those noted after ninety days, but marginally less severe. Additionally, in the lungs, a few of the foamy macrophages containing pigment were present in the peribronchial lymphoid cuffs, a feature not present after ninety days exposure. In the nasal cavity, submucosal pigment deposition was present at most levels in nearly all high dose rats, but appeared to be slightly less severe than was noted after ninety days. In the tracheobronchial lymph nodes, hyperplasia of foamy macrophages containing a minimal amount of pigment was slightly more severe than was noted after ninety days exposure. Lymphoid hyperplasia was essentially comparable. In the kidney tubules, the increased tubular pigment was less severe than was noted after ninety days. In the liver, pigment deposition in the bile duct epithelium was comparable to that noted after ninety days exposure.

In the rats exposed to Solvent Yellow-Green Dye Mixture at $10~\text{mg/m}^3$ for ninety days followed by a thirty-day recovery period, only

lung, nasal cavity, tracheobronchial lymph node, liver and kidneys were examined. Lesions similar to those noted at this level after ninety days exposure were present. Minimal lung lesions were noted in two rats of each sex and submucosal pigment deposition was noted in the nasal cavity of single rats of each sex at Level II, six males and five females at Level III, and two males and six females at Level IV. In the tracheobronchial lymph node, of one male, lymphoid hyperplasia was present, but hyperplasia of foamy macrophages was not present in any of the lymph nodes examined. Pigment deposition in the kidneys was comparable to the controls and no pigment deposition was noted in the liver.

No compound-related histomorphologic alterations were noted in the lung and nasal cavity of rats exposed to 1 mg/m^3 for ninety days followed by a thirty-day recovery period.

Spontaneous disease lesions and incidental findings occurred in rats in both control and treated groups at both sacrifice intervals.

These lesions were distributed with approximately equal frequency in test and control rats.

CONCLUSIONS

Exposure of rats to Solvent Yellow-Green Dye Mixture at 100 mg/m³ for six hours/day, five days/week for thirteen weeks resulted in accumulations of foamy alveolar macrophages containing minimal amounts of pigment in the lungs. These accumulations were accompanied by hyperplasia of Type II pneumocytes. Similarly, foamy macrophages

with pigment had accumulated in the tracheobronchial lymph nodes.

Pigment deposition was noted in the nasal cavity, liver, and kidney.

After a thirty-day recovery period these lesions were decreased in severity with the exception of foamy macrophages in the tracheobronchial lymph nodes which were slightly increased.

Exposure of rats to Solvent Yellow-Green Dye Mixture at 10 mg/m³ resulted in only minimal lesions in the lungs and tracheobronchial lymph nodes of a few rats and pigment deposition in the nasal cavity to a much lesser degree than was noted at the high dose exposure. After a thirty-day recovery period, these minimal lesions were essentially unchanged.

Exposure of rats to Solvent Yellow-Green Dye Mixture at 1 mg/m^3 did not result in any compound-related histomorphologic changes in the tissues examined.

DEBORAH A. BANAS, D.V.M., M.S. Veterinary Pathologist

8/13/85

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QUALITY ASSURANCE REPORT CERTIFICATION

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	Lovelace Inhalation Toxicology Research Institute Client Study No. RZ-75
Study Directo	r <u>Dr. Larry Ackerman</u> Pathologist <u>Dr. Deborah Banas</u>
Study Title _	90 Day Repeated Inhalation Exposures of Rats to Solvent Yellow-Green Dye Mixture
Test Article	Solvent Yellow-Green Dye Species Rats
All parts	of the pathology phase of this study, including the final report,
were revie	wed by Experimental Pathology Laboratories Quality Assurance Unit
on <u>April</u>	10, 1985 through August 13, 1985 . All findings were reported
to the Stu	dy Director and Management.
	Janet Milaya 8/13/85
	8/13/85

NINETY-DAY SACRIFICE
SUMMARY INCIDENCE TABLES

RZ-75 90 Day Sacrifice Male Rats

	Group	Group 0	Group M	Group N	
LUNG (NO. EXAMINED)	. (10)	(10)	(10)	(10)	i
Accumulations of Foamy					
Macrophages		10		2	
Hyperplasia of Type II Cells		10		1	
Pigment Deposition		10		3	
Adhesion	:				
Hemorrhage				2	
Peribronchial Lymphoid					
Hyperplasia	10	10	8	10	
NASAL CAVITY-LEVEL I					
(NO. EXAMINED)	(10)	(10)	(10)	(10)	
Hemorrhage		3	11	1	
Submucosal Pigment Deposition	:	8	 .	· · · · · · · · · · · · · · · · · · ·	
Congestion					
Serous Exudate					
Foreign Material					
Nonsuppurative Rhinitis			1		,
Cystic Glands			1		
NASAL CAVITY-LEVEL II	· · · · · · · · · · · · · · · · · · ·	 			
(NO. EXAMINED)	(10)	(10)	. (8)	(9)	
Hemorrhage		2	1		
Submucosal Pigment Deposition		10		:	
Inflammation of Nasolacrimal	!				
Duct	i '	4			·
Foreign Body	!	1		1	i
Focal Squamous Metaplasia		1			
Focal Inflammation	1	1	:		
Congestion	1			1	!

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RZ-75 90 Day Sacrifice Male Rats

	Group L	Group O	Group M	Group N	. !
CSAL CAVITY-LEVEL II (CONTINUED)		!		<u> </u>	· · · · · · · · · · · · · · · · · · ·
Serous Exudate		: !		 	!
Nonsuppurative Rhinitis		<u>:</u>	i 	<u> </u>	
Cystic Glands		 	. 1		ì
SAL CAVITY-LEVEL III	: :	·	· · · · · · · · · · · · · · · · · · ·	·	·
NO. EXAMINED)	(10)	(8)	(9)	(9)	
-Hemorrhage	1		1		
Submucosal Pigment Deposition	<u> </u>	8		1	·
-Serous Exudate					
- Jei ous Exada te		-			•
ASAL CAVITY-LEVEL IV	 				
O. EXAMINED)	(10)	(10)	(9)	(8)	
	1				
Hemorrhage		10			
Submucosal Pigment Deposition					
Serous Exudate			<u> </u>		
TO ACUE OPPONICHT AL			. —		
LIMPH NODE, TRACHEOBRONCHIAL	(7)	(10)		(10)	
(NO. EXAMINED) ∴Hyperplasia of Foamy					
		 9		2	
Macrophages		<u></u>			
Lymphoid Hyperplasia		10 10		2	
Pigment Deposition	<u>-</u>		3		·
Hemorrhage	·				
MIDNEY (NO. EXAMINED)	(10)	(10)		(10)	
Regenerative Tubular					· · · · · · · · · · · · · · · · · · ·
. Epithelium	. 5	6		6	<u> </u>
Casts		3	·	1	<u> </u>
Cortical Infarct		1		: 	<u> </u>
· .		I-2			
		- -			
PL PL	100				
Experimental Pathology Laboratories	. Inc				

RZ-75 90 Day Sacrifice Male Rats

	Group	Group	Group	Group N	
KIDNEY (CONTINUED)	<u> </u>	<u>. </u>			
Foci of Mononuclear Cells		. 3	·	1	
Pigment Deposition	10	10		10	
LIVER (NO. EXAMINED)	(10)	(10)	···	(10)	
Bile Duct Hyperplasia	1				
Foci of Mononuclear Cells	2	. 3		2	
Cholangiofibrosis	1				
Pigment Deposition		10			
BRAIN (NO. EXAMINED)	(10)	(10)			
PITUITARY (NO. EXAMINED)	(10)	(8)			
ADRENAL (NO. EXAMINED)	(10)	(10)			
Kemorrhage	1				
Vacuolated Cortical Cells		1			
EYE (NO. EXAMINED)	(10)	(10)			
Corneal Subepithelial					
Basophilia		1	-		
THYROID (NO. EXAMINED)	(9)	(9)			
LARYNX (NO. EXAMINED)	. (9)	(9)	·	-	
Foci of Mononuclear Cells		2	· · · · · · · · · · · · · · · · · · ·		
			·		· · · · · · · · · · · · · · · · · · ·
	i	<u>:</u>		·	
	:	:	:		:

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RZ-75 90 Day Sacrifice Pale Rats

	Group	Group 0	: Group ; M	Group N	
TRACHEA (NO. EXAMINED)	(10)	(10)	;	 	İ
- Hemorrhage	1		!	:	1
TEART (NO. EXAMINED)	(10)	. (10)		:	· .
Nonsuppurative Myocarditis	8	3		 	··
Pigment Deposition	1				
SPLEEN (NO. EXAMINED)	(10)	(10)			
ic					
PANCREAS (NO. EXAMINED)	(10)	(10)			
<u>;</u>					
LYMPH NODE, POPLITEAL					
NO. EXAMINED)	(7)	(9)			
STOMACH (NO. EXAMINED)	(10)	(10)			
DUODENUM (NO. EXAMINED)	(10)	(10)			
CECUM (NO. EXAMINED)	(10)	(10)		-	
Nematodiasis	4	4			
COLON (NO. EXAMINED)	(10)	(10)			
Nematodiasis		3			
SKIN (NO. EXAMINED)	(10)	(10)			
ESTIS (NO. EXAMINED)	(10)	(10)			
Atrophy	1	1			
,		<u>i</u>		· · · · · · · · · · · · · · · · · · ·	

RZ-75 90 Day Sacrifice Male Rats

	, Group L	Group O	Group M	Group N	
EPIDIDYMIS (NO. EXAMINED)	(10)	(10)			
Spermatic Granuloma		1			
Aspermia	1	1			
PROSTATE (NO. EXAMINED)	(10)	(9)			
Nonsuppurative Prostatitis	1				
URINARY BLADDER (NO. EXAMINED)	(10)	(10)			
FEMUR (NO. EXAMINED)	(10)	(9)			
ADIPOSE TISSUE (NO. EXAMINED)		(10)			
STERNUM (NO. EXAMINED)	-	(1)			
			·		
	· · ·	•			
		· · · · · · · · · · · · · · · · · · ·			
	. _		· · · · · · · · · · · · · · · · ·	<u> </u>	
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	<u>.</u>				·
		<u>:</u> <u></u>	····		.
		•	·	:	

RŽ-75 90 Day Sacrifice male Rats

	Group L	Group 0	Group M	Group N	
MING (NO. EXAMINED)	(10)	(10)	(10)	(10)	
Accumulations of Foamy		: :			
Macrophages	i	10		3	
Hyperplasia of Type II Cells	!	10		1	
Pigment Deposition	:	10		i 3	
	1	ì	-	! .	···
Hemorrhage	I	`			:
Peribronchial Lymphoid	:			:	I
Hyperplasia	8	10	6	7	:
ASAL CAVITY-LEVEL I					·
(NO. EXAMINED)	(9)	(10)	(10)	(10)	
Hemorrhage					
Submucosal Pigment Deposition		4		·	•
Congestion	1	- 			
Serous Exudate	ì				
Foreign Material		1			
Nonsuppurative Rhinitis					
Cystic Glands					
NASAL CAVITY-LEVEL II					
NO. EXAMINED)	(9)	(10)	(8)	(9)	
Hemorrhage	·— - — · · · · ·			- . - ·	:
Submucosal Pigment Deposition		10		· 	
Inflammation of Nasolacrimal					
. Duct	1	2	:		
Foreign Body		:			
. Focal Squamous Metaplasia	· · · · · · · · · · · · · · · · · · ·			-	
Focal Inflammation		1	_ _	· · · · · · · · · · · · · · · · · · ·	
Congestion	1		1	í	

1-6

RZ-75 90 Day Sacrifice Female Rats

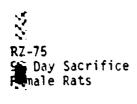
!	Group L	ı	Group 0	Group M	Group N	
NASAL CAVITY-LEVEL II (CONTINUED)						
Serous Exudate	1					
Nonsuppurative Rhinitis		:		· 		·
Cystic Glands						
NASAL CAVITY-LEVEL III						
(NO. EXAMINED)	(9)		(10)	(10)	(9)	
Hemorrhage					· 	
Submucosal Pigment Deposition			10		4	
Serous Exudate	1					
NASAL CAVITY-LEVEL IV						
(NO. EXAMINED)	(9)		(10)	(5)	(7)	
Hemorrhage						
Submucosal Pigment Deposition			10		2	
Serous Exudate	1					
LYMPH NODE, TRACHEOBRONCHIAL						
(NO. EXAMINED)	(6)		(8)	(6)	(8)	
Hyperplasia of Foamy						
Macrophages			8		2	:
Lymphoid Hyperplasia	1		8			:
Pigment Deposition		!	8	_	2	
Hemorrhage					1 2	!
		i		<u>i</u>	!	
KIDNEY (NO. EXAMINED)	(10)	<u> </u>	(10)	·	(10)	
Regenerative Tubular	 	i -			<u> </u>	
Epithelium					<u>!</u>	
Casts	<u> </u>	<u></u>		! !		
Cortical Infarct	i 			! 	i	<u> </u>

RZ-75
Day Sacrifice
male Rats

	Group	Group O	Group M	Group N	
DNEY (CONTINUED)					
Foci of Mononuclear Cells	1	2			i
Pigment Deposition	3	10		8	l
·			1		
IJVER (NO. EXAMINED)	(10)	(10)	(10)	(10)	·
Bile Duct Hyperplasia			1	1 1	·
Foci of Mononuclear Cells			5	4	
Cholangiofibrosis		1	İ		!
Pigment Deposition	1	10	:	2	·
		!	!	· '	
ERAIN (NO. EXAMINED)	(9)	(10)	<u> </u>		
		1		1	
TUITARY (NO. EXAMINED)	(8)	(10)		1	
			<u>:</u>	· .	
FRENAL (NO. EXAMINED)	! (10)	; (10)		:	·
Hemorrhage				:	
Vacuolated Cortical Cells					
	:	ı	:	·	
FE (NO. EXAMINED)	(9)	(10)	(
Corneal Subepithelial,	i			i I	
- Basophilia		1	į	!	! !
			!	İ	
THYROID (NO. EXAMINED)	(10)	(9)			:
LARYNX (NO. EXAMINED)	(10)	(9)			!
Foci of Mononuclear Cells		2			
•					<u> </u>
3					
ii.					
					i

RZ-75 90 Day Sacrifice Female Rats

	Group	Group	Group	Group N	· :	
TRACHEA (NO. EXAMINED)	(10)	(10)	1	1	· · · · · · · · · · · · · · · · · · ·	
Hemorrhage		i	:			
HEART (NO. EXAMINED)	(10)	(10)				<u>[</u>]
Nonsuppurative Myocarditis	1	1	1	į		
Pigment Deposition	!				·	
SPLEEN (NO. EXAMINED)	(10)	(10)		· ,	·	
PANCREAS (NO. EXAMINED)	(10)	! (10)	·			
LYMPH NODE, POPLITEAL		··-·	 	; 		
(NO. EXAMINED)	(7)	(8)	<u> </u>	•		
STOMACH (NO. EXAMINED)	(10)	(10)	;			
DUODENUM (NO. EXAMINED)	(10)	(10)	<u>:</u>	1		
CECUM (NO. EXAMINED)	1 (10)	(10)	1			
Nematodiasis	4	1	! 			· <u>·</u>
COLON (NO. EXAMINED)	(10)	(10)	Ì			e
Nematodiasis	2	2		1 1	· ·	 :
SKIN (NO. EXAMINED)	(10)	(10)				
OVARY (NO. EXAMINED)	(9)	(10)			:	
						



Group '	Group O	Group M		N	
(9)	(10)				
2	1				
					:
(8)	(10)				
					
(10)	(10)				
	(8)				
					<u></u>
				-	
		-			
					
			— - - -		
	.	—			
	<u>.</u>	<u> </u>			
	_	<u>.</u>			
. .			-		<u>.</u>
<u>. </u>					<u> </u>
······································					
	(9) 2 (8) (10)	L 0 (10) 2 1 (8) (10) (10) (10) (8)	L 0 M (9) (10) 2 1 (8) (10) (10) (10)	L 0 M (9) (10) 2 1 (8) (10) (10) (10)	L 0 M N (9) (10) 2 1 (8) (10) (10) (10)

NINETY-DAY SACRIFICE

7

HISTOPATHOLOGY INCIDENCE TABLES

GROUP	(mg/m3)	TREATMENT
L	0	Controls
M	1	Low Exposure Concentration
N	10	Medium Exposure Concentration
0	100	High Exposure Concentration

:

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M

RZ-75 90 Day Sacrifice Male Rats			_			Gr	oup) L													
	A N U I M B A E L R	3 7 3 1 - 0 0 9	3 7 3 1 - 0 1 0	3 7 3 1 - 0 1	3 7 3 1 - 0 1 2	3 7 3 1 - 0 1 3	3 7 3 1 - 0 1 4	3 7 3 1 - 0 1 5	3 7 3 1 0 1 6	3 7 3 1 - 0 1 7	3 7 3 1 - 0 1 8										
LUNG															 .	_					
Accumulations of Foamy		↓		-			-	_		. .					_	_					
Macrophages		ļ											_					_		 .	
Hyperplasia of Type II Cells		<u> </u>		_					- .								• • -				
Pigment Deposition		ļ					-		<u></u> .				_								
Adhesion								_				_		_			_~_		_		
Hemorrhage		 								_			Ţ		_	_	_	. . .			
Peribronchial Lymphoid		<u> </u>	-	.		_				. 											
Hyperplasia		2_	1	. 2	1	1	, 1	1	. 1	. 1	. 1	-				-		-			-
NASAL CAVITY-LEVEL I		X	X	X	X	X	X	X	_ X	X	χ.	•		•	-						
Hemorrhage									-	-	-										. –
Submucosal Pigment Deposition	n			•						-	•				•	•	-	-	•		
Congestion			_		•		-		•	-		•		•			-		•		
Serous Exudate]		•	-					-	-	-	-				•			•	
Foreign Material		1	-		•	-	-	-	•		-	•									-
Nonsuppurative Rhinitis		1									_	•	-								-
Cystic Glands		1	-	-	-			-	-		-		-		-		-	•			•
		1	-	-	-		-		-		•	-					•		•		-
NASAL CAVITY-LEVEL II	-	1 x	 X	. <u>.</u>	X	X	X	X	X	X	X	-	•		•	•					
Hemorrhage		1 "	- "	- ''	.,	•		. ••			- ' '				•						
Submucosal Pigment Depositio	 ח		-	-	-			-	-	•											
Inflammation of Nasolacrimal				•	•			•		•	-										
Duct		1 -	-	•	•		•	•							•						
Foreign Body		1	-	•										•							
Focal Squamous Metaplasia				•	•				•	•			•	•	•						
		1	-	•	•				•	•	•	•	•	•		٠				٠	÷
Focal Inflammation						· 	· 		· 		-	· 	-			· 					

EPL

ZZ-75 90 Day Sacrifice Male Rats						Gr	oup	L													
		3	3	3	3	3	3	3	3	3	3										
	A N N U I M M B	3	3 7 3 1	7 3 1	7 3 1	3 7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1										
•	A E L R	1009	0 1 0	0 1 1	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	0 1 7	018										
ASAL CAVITY-LEVEL II (CONTINU		Ĭ .				-				-											
Congestion Serous Exudate																				,	•
Serous Exudate Nonsuppurative Rhinitis									-	-	-	•	-	-	•				-	-	
Cystic Glands											_			-	-	•	•	-	*	-	
ASAL CAVITY-LEVEL III Hemorrhage		l							X		. 2		•								
Submucosal Pigment Depositio		ì							-	•		•	-	•	٠		-		-	•	
, _		l									-				=						
ASAL_CAVITY-LEVEL IV Hemorrhage		1						X	X		. 2				•						-
Submucosal Pigment Depositio																					
Serous Exudate			_								-	-	-		٠	-					-
YMPH NODE, TRACHEOBRONCHIAL Hyperplasia of Foamy		N	. X	N	X	X	X	X	N	X	X	-	=		-						
Macrophages		ļ · · ·	-		-										•	•	-				
Lymphoid Hyperplasia Pigment Deposition	•		-	-	•			-		•											
Hemorrhage			-																		
IDNEY																					
Regenerative Tubular																					
Epithelium	-		1	1	1	1				•	, 1		-		-						

Experimental Pathology Laboratories, Inc.

Key P - Present N - No Section A Aurily S X - No Formarkable 3 - Millian 3 - Sight 3 - Millian 4 - Millian 4 - Millian 5 - Severe might 1 - inclume at Exection

RZ-75 90 Da Socrifice Group L Male Rats 0 1 1 1 1 1 0 4 5 6 7 0 KIDNEY (CONTINUED) Cortical Infarct Foci of Mononuclear Cells Pigment Deposition 1 1 1 1 1 1 1 1 1 IVER Bile Duct Hyperplasia Foci of Mononuclear Cells Cholangiofibrosis Pigment Deposition BRAIN \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} PITUITARY \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{X} \mathbf{x} \mathbf{x} \mathbf{x} \mathbf{x} \mathbf{x} \mathbf{x} ADRENAL Hemorrhage Vacuolated Cortical Cells Corneal Subepithelial ___Basophilia___ THYROID X X X X X X X X X X

11-3

EPL Experimental Pathology Laboratories, Inc

Key P = Present 1 = Minimat 2 = Sight 2 = Sight 1 = incomplete Section

A N	3											
M B A E L R	7 3 1 - 0 0 9	3 7 3 1 - 0 1 0	3 7 3 1 0 1	3 7 3 1 - 0 1 2	3 7 3 1 - 0 1 3	3 7 3 1 - 0 1 4	3 7 3 1 - 0 1 5	3 7 3 1 - 0 1 6	3 7 3 1 - 0 1 7	3 7 3 1 - 0 1 8		
	X	χ	X	X	, X	X	X	N	X	X		
				-	-							1
	X 	X	- X	2	X	X .	_ X	- , X 	X	X .		
			-			~	•	. .		v		
	2	1	. 1	^	1	. 1	1	1	2	^		·· <u>-</u> ·
	x	_ X	_ X	X	X	X	x	x	X	X		
	x	X	X	X	X	. X	X	X	X	X		
	×	. X	X	. X	X	. X	N	N	X	N		
	X	` X	X	X	X	X	X	X	X	X	**	
	×	X	X	X	X	X	X	X	X	X		
	X	, X	P	P	P	X	X	X	X	Р		
· ·	X	X	X	X	X	X	X	X	X	X		
	M B A E L R	X X X X X X X X	X X X X X X X X X X X X X X X X X X X	X X X X X X X X X X X X X X X X X X X	X X X X X X X X X X X X X X X X X X X	A E O O O O O O O O O O O O O O O O O O	A E O O O O O O O O O O O O O O O O O O	A E O O O O O O O O O O O O O O O O O O	X X X X X X X X X X X X X X X X X X X	A E O O O O O O O O O O O O O O O O O O	A E O O O O O O O O O O O O O O O O O O	A

11-4

E P L Experimental Pathology Laboratories, Inc

Key P+ Fresent N+N Section
1 + Morma 2 + Sight
5 + Severe High 1 + 50 - 60 to Sec

A reacting common type Burner (Apt 4) - 3 ft Milgorian (Apt 2) in the Consense of the

RZ-75 90 Day Sacrifice Male Rats

Group L

Male Rats		ſ						• •											 	 	ì
	N I M A	N U M B E R	3 7 3 1 - 0 9	3 7 3 1 - 0 1 0	3 7 3 1 - 0 1	3 7 3 1 - 0 1 2	3 7 3 1 - 0 1 3	3 7 3 1 - 0 1 4	3 7 3 1 0 1 5	3 7 3 1 0 1 6	3 7 3 1 - 0 1 7	3 7 3 1 - 0 1 8	, ,								
SKIN			X	X	X	_ X	X	X			X						-				15
TESTIS Atrophy			X	X	5		X	- X	_ X	_ X	X 	X	- : : :			-				 . <u></u>	
EPIDIDYMIS Spermatic Granuloma			X	X		 _ X -	т х х	- _ X 	X	_ X	X	X	-					-	· ·		
Aspermia		_			- <u>-</u>				•	. .		- ·-	-	-			•		 	<u>.</u>	1.
PROSTATE Nonsuppurative Prostatitis	- - -		X	_ X 	X	. X	1	, X	X	. X	X	X			-		-	 	-	· -	
URINARY BLADDER	· — ·		X	 _ X	- _ X	. X	X	X	. X	X	X	. X									1
FEMUR			X	_ X	X	X	X	- X	X	X	X	X					-				
				- 	-																
				-																	
									•							-					
				-			*														
				-]].

11-5

EPL Experimental Pathology Laboratories, Inc

Key P = Present N = No Section
1 = Vinmat 2 = Sight
5 = Severe High 1 = incomplete Sec

\$2-75 \$0 Day Sacrifice Male Rats					Gr	oup	0								 		
X																	
A N U I M B	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4		3 7 3 4		3 7 3 4	3 7 3 4	3 7 3 4							
A E L R	00	0	0	0	0	0	0	0	0	0							
UNG	9_	_0_	_1_	_2_	_3_	4_	5	6_		8					 		
Accumulations of Foamy			- •	•		-								-			-
• Macrophages	2	- २	. 2	. 2	2	2	3	2	2	2					•		
Hyperplasia of Type II Cells	7 -	-							•		-					-	
Pigment Deposition	1			1						1					-	-	
Adhesion	-	-					•	•	•			-		٠			
Hemorrhage	1			-						-			-				
Peribronchial Lymphoid	1		-								•						
Hyperplasia	2	1	1	2	1	2	1	1	1	, 2			-				
NASAL CAVITY-LEVEL I			-		2		X		2					-			
Submucosal Pigment Deposition	1	1		1	•	1		1	2	2							
Congestion	-	. -	. .			•		-	-								
Serous Exudate	1																
Foreign Material											-						
Nonsuppurative Rhinitis	1																
Cystic Glands	Ì			÷													
NASAL CAVITY-LEVEL II	1																
Hemorrhage	1			-						2							
Submucosal Pigment Deposition	2	2	2	1	3	2	2	2	2	3							
1. Inflammation of Nasolacrimal								_									
Duct			2		2	2		2									
Foreign Body	1						P										
Focal Squamous Metaplasia	}						2				·						
Focal Inflammation	<u> </u>						3								 		

11-6

RZ-75 90 Day Sacrifice Male Rats	 -	_			Gr	oup	0			-	
A N N U I N M B A E L R	3 4	3 7 3 4 - 0 1	-	3 7 3 4 - 0 1		3 7 3 4 - 0 1 4				3 7 3 4 - 0 1 8	
NASAL CAVITY-LEVEL II (CONTINUED)									<u>`</u> _		
Congestion	7"				_		_	_			
Serous Exudate							_	_	_		
Nonsuppurative Rhinitis	<u>.</u>	-	_						_		
Cystic Glands	.			_	. · · · ·		-	-	÷		
NASAL CAVITY-LEVEL III		· -				 N	N		-		
Hemorrhage	_									_	
Submucosal Pigment Deposition Serous Exudate	4	. 4	. 4	3	4			4	3	4	
NASAL CAVITY-LEVEL IV Hemorrhage	-	•	-								
Submucosal Pigment Deposition Serous Exudate	4	2	_1	3	3	3	. 3	2	4	. 4	
LYMPH NODE, TRACHEOBRONCHIAL	1		- •		,		•	•		-	• · · · •
_Hyperplasia_of_Foamy				_					_		
Mac rophages	2	1	2	3	2	2		2	1	3	
Lymphoid Hyperplasia	2	2	_ 3	4	4	4	2	2	3	4	
Pigment Deposition Hemorrhage	1	1	1	. 1	1	1	1	1	1	1	
KIDNEY											
Regenerative Tubular							-				
Epithelium		1	2	1	1			1		1	

11-7

E P L Experimental Pathology Laboratories, Inc

Casts

P = Present N = N, Socton
1 = M n ma 2 = Sight
5 = Severe High 1 = course (in

A = Autogood () = Not Equipment = 3 = Not go are () Sever

原Z-75 始O Day Sacrifice Male Rats		p			··	Gr	oup	0												
	A N N U I M M B A E	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4									
	L R	0 0	0 1 0	0 1	0 1 2	0 1 3	0 1 4	0	0	0 1 7	0 1 8									
IDNEY (CONTINUED)		_				_ 								_		<u>,</u>				
Cortical Infarct		2																		
Foci of Mononuclear Cells			1		_					1	. 1	_		:					-	
Pigment Deposition		3	_ 3 _	_ 3	. 3	. 2	_ 2,	_ 3	. 3	_ 3 ,	_ 3			-						
L. L. L. L. L. L. L. L. L. L. L. L. L. L				-			· ·							÷		-	-			
Bile Duct Hyperplasia		-		•				-		• -	٠		•			-	•			
Foci of Mononuclear Cells		1	•	1	-	•	• •	1	-	-						-	٠	•		
Cholangiofibrosis		1		. •			•	•				•			-					
Pigment Deposition		1	1	1	1	1	1	1	1	1	1				•	-	-			·
RAIN		<u>x</u>	- _, X	X	. X	. X	- , X	, X	. X	X	X				_			-		
\(\frac{1}{2} \)			-					,												İ
PITUITARY		N	. X	. X	X	, X	X	N	X	X	, X									-
ADRENAL			 _ X	X	X	X	X	X	- X	- . X	_ X			٠						
Hemorrhage															-					}
		2					-													
ILYE		1	Y	¥	X	X	X	X	X	X	X									
· Corneal Subepithelial			. "	. "	•		. "	•		•		•								1
Basophilia		2	-	•																
HYROID		X	X	, X	X	N	X	X	X	X	X									
	_	-	-																	
Ý.		-	<u>.</u>	-			-													
<u> </u>		1																		

11-8

EPL Key P=Present N=1, Sector All Auto Subtractions of the Minimal 2=5 grid 3=Multiple 4=Minimal 2=5 grid 3=Multiple 4=Minimal

RZ-75 90 Day Sacrifice Male Rats

Group O

	A N U I M B A E L R	3 7 3 4 - 0 0 9	3 7 3 4 - 0 1 0	3 7 3 4 - 0 1 1	3 7 3 4 - 0 1 2	3 7 3 4 - 0 1 3	3 7 3 4 - 0 1 4	3 7 3 4 - 0 1 5	3 7 3 4 - 0 1 6	3 7 3 4 - 0 1 7	3 7 3 4 - 0 1 8										
LARYNX		X		X	_ X	N	X	- <u>-</u> -	X_	X.	X										
Foci of Mononuclear Cells		-	1					_1_				-			- · -						
TRACHEA		X	X	X	X	X	X	_ X _	X	X	X					_	_				
Hemorrhage					-		_		.	-				-					-		
HEART				X	X	X		X	X	X	χ.	-	· ·						-		
Nonsuppurative Myocarditis		1	2			-	_1			 -		- · · · -									
Pigment Deposition				-	-				÷				-	-							
SPLEEN		X	X	X	_ X	X	, X	. X	_ X	X	X	-				-					
PANCREAS		X	X	X	X	_ X	X	X	. X	. X	X	-		-		-		ė			
LYMPH NODE, POPLITEAL		X	X	X	_ _ X	X	N	. X	X	 . X	_ X	-	- -	•							-
STOMACH	-	X	χ	 . X	. X	. X	. X	X	. X	X	X			-							•
DUODENUM		X		 _ X	 , X	X	X	X	, X	X	- X	-									
CECUM	•		 X		- X		•	X	X	X	X										
Nematodiasis		P	. "	P		Р	. P														
COLON	_		- ·	X		X	X	X	X	X	X										
Nematodiasis		P	Р		_ P			-						·	-						İ
			••	· · ·	•		•			٠			•							-	1

ズ2-75 ろり Day Sacrifice Male Rats						Gr	oup	0				
	Á N	3 7	3 7	3 7	3 7	3 7	3 7	3 7	3 7	3 7	3 7	
	N U I M M B A E	3 4 -	3 4 -	3 7 3 4 - 0	3 4 - 0	3 7 3 4 - 0	3 4 - 0	-	3 4 -	3 4	3 4 -	
··-	L R	0 0 9	1 0	1	1 2	1 3	1 4	0 1 5	1 6	1 7	1 8	
KIN						X	٠.					
Atrophy		-		.			-		, X	- . 5 <u>.</u>		
PIDIDYMIS Spermatic Granuloma		X	_ X	_ X	. X	X	, X	- , X	P		, X	
Aspermia		}								P		
PROSTATE Nonsuppurative Prostatitis	- ·	X	_ X	N	X	X	X	X	X	X	X	
RINARY BLADDER		X	X	X	. X	_	X	X	X	. X	. X	- · · · · · · · · · · · · · · · · · · ·
FEMUR	-]	_		-	X					-	•
ADIPOSE TISSUE		1				X						
STERNUM				, X		•						
			• •									
		1_							-			

11-10

Experimental Pathology Laboratories, Inc.

A = Automorphism = to the complete endings are also the complete endings. A = M = to the complete endings.

RZ-75 90 Day Sacrifice Male Rats						Gr	oup	M														7
	A N N U I M M B A E L R	3 7 3 2 - 0 9	3 7 3 2 - 0 1 0	3 7 3 2 - 0 1 1	3 7 3 2 - 0 1 2	3 7 3 2 - 0 1 3	0	3 7 3 2 - 0 1 5	- 0 1	3 7 3 2 0 1 7	0											
LUNG						_	_	X		X			_	_		,.						
Accumulations of Foamy			•	- -		.		··-			_						_	. . .	_			
Macrophages		\mathbb{L}_{-}									_			,					_			
Hyperplasia of Type II Cell	s					- · -					_				- ·	_		-	-			
Pigment Deposition				_					_								_		_	- '		
Adhesion				-	-				-			-		-				•	-			
Hemorrhage]		-	-							•	•	•		•		•	•	•	-	
Peribronchial Lymphoid				•	•		-	-	-	-			-			-		-	•	•		
Hyperplasia		1	1	1	1	1	1	-	1	•												
							-						-	-		• • • •		•			•	1
NASAL CAVITY-LEVEL I	•		X	X	X	X	X		X	X	X				• • • •		•			-		
Hemorrhage		1						1	•			•	•	•	• • •	-	•				-	
Submucosal Pigment Depositi			_		-																-	
Congestion		1	•				-		-					٠	-	•					•	
Serous Exudate										•	•	-	•	_	_		•					1
Foreign Material		1				•	-	•	•	•	•			•		•						1
Nonsuppurative Rhinitis		1	•			•	-	-		•	•		-			-	-					1
Cystic Glands		1	-				-	1					-									
		1	-		•	•					•				٠							1
NASAL CAVITY-LEVEL II		1 x	X	X	N	X	N		X	X	X				-							1
Hemorrhage		"	. ••	-•	- ·•	••	•	2	. **		• •					•						
Submucosal Pigment Depositi	on							-														
Inflammation of Nasolacrima				•		•																
Duct	•														٠							
Foreign Body									•													
Focal Squamous Metaplasia						÷									٠							1
Focal Inflammation		1	•	•			•						•	•							Ť	
rocal initialianation		ــــــــــــــــــــــــــــــــــــــ																				ل

11-11

EPL Experimental Pathology Laboratories, Inc

Key P = Present N = N = N = Section
1 = M numa 2 = Sight
5 = Severe High 1 = Incomplete Sec

All-Autritysis (IIII) + Nuit Remarkable 3 - Nugorate (IIII) 4 - Miliperate / Severe (IIII)

NZ-75 90 Day Sacrifice pale Rats	F				Gr	onb	М									 	
A N N U I M M B A E L R	3 7 3 2 - 0 9	3 7 3 2 0 1 0	3 7 3 2 - 0 1 1	3 7 3 2 - 0 1 2	3 7 3 2 - 0 1 3	3 7 3 2 - 0 1 4	3 7 3 2 - 0 1 5	3 7 3 2 0 1 6	3 7 3 2 - 0 1 7	3 7 3 2 - 0 1 8	 			·			
Congestion Serous Exudate Nonsuppurative Rhinitis		- 	-	-	–		• . •	<u>.</u> .			 -	•••	-			 - -	
Cystic Glands ASAL CAYITY-LEVEL III Hemorrhage Submucosal Pigment Deposition	N	 , X	 X	X	X		. 3		X	X				•			
Serous Exudate ASAL CAVITY-LEVEL IV	_ x	- N		- X	X	X	3	X	X	X	•		•		•		
Submucosal Pigment Deposition Serous Exudate LYMPH NODE, TRACHEOBRONCHIAL	X	. X	X		X	N		X	X								
Hyperplasia of Foamy Macrophages Lymphoid Hyperplasia Pigment Deposition							2										
Hemorrhage							2			1							
		•								· —						 ·	

11-12

PA EPL

Experimental Pathology Laboratories, Inc.

RZ-75 90 Day Sacrifice Male Rats						Gr	oup	N														
	A N U I M M B A E L R	3 7 3 3 - 0 9	3 7 3 3 - 0 1 0	3 7 3 3 - 0 1 1	3 7 3 3 - 0 1 2	3 7 3 3 0 1 3	3 7 3 3 0 1 4	3 7 3 3 - 0 1 5	3 7 3 3 - 0 1 6	3 7 3 3 - 0 1 7	3 7 3 3 - 0 1 8											
LUNG									-	-		_	- -		-							1
Accumulations of Foamy						-		-	- - -		_					_	_	-				
Macrophages							_1		1	-	_				_							1
Hyperplasia of Type II Cells	<u> </u>						1												-			-
Pigment Deposition	<u> </u>		_ 1		-		1		1						-				-			.
Adhesion								-				-				-			-	-		┨.
Hemorrhage		1	. 1			-			-				-	-			-			-		┦:
Peribronchial Lymphoid		_						-				· -						-		<u>.</u>		4.
Hyperplasia		1	2	. 1	2	1	. 1	1	. 1	1	. 1			-								1
NASAL CAVITY-LEVEL I	-	X			 X	X	X	X	X	 X	X	-			-	-						
Hemorrhage		1	1	-			•		-						-	•			-	-		
Submucosal Pigment Deposition	n —						-								•						•	1
Congestion				•	-	-	•						•			•						
Serous Exudate			-	-	•					•	• •	-		-					-	٠	-	1
Foreign Material			-	•					•	•		•	•	-	•							
Nonsuppurative Rhinitis						•	•				•			•]
Cystic Glands					_															-		
			-																			
NASAL CAVITY-LEVEL II		X	X	, X	, N		X	X	X	X	X											
_Hemorrhage																						1
Submucosal <u>Pig</u> ment Deposition	on _.																					
Inflammati <u>o</u> n of Nasolacrimal																						
Duct																					-	
Foreign Body		_				-																ł
Focal Squamous Metaplasia				-																		-
Focal Inflammation													_									

II-13

E P L Experimental Pathology Laboratories, Inc.

Key P = Present Nin No Section
1 + Min ma 2 + 5 ght
5 - Severe High 1 - Incomprete Section

Al-Agragos — Nertur Pemarkat e 3 m Modelate — 4 m Milderate y Severe

ŸÕ Day Sacrifice Male Rats		<u> </u>				ur ——	oup					
	A N U I M B A E L R	3 7 3 3 - 0 0 0	3 7 3 3 0 1	3 7 3 3 - 0 1	3 7 3 3 - 0 1	3 7 3 3 - 0 1	3 7 3 3 - 0 1	3 7 3 3 - 0 1 5	3 7 3 3 - 0 1	3 7 3 3 - 0 1	3 7 3 3 - 0 1	
ASAL CAVITY-LEVEL II (CONTINU Congestion		1										
Serous Exudate		ļ	.	-	. . ,					•	-	
Nonsuppurative Rhinitis Cystic Glands		-				1.			.	-		
MASAL CAVITY-LEVEL III		x	X			X	X	X	, X	N	, X	
Hemorrhage Submucosal Pigment Depositio Serous Exudate	n	-		_ 1		. –	_				•	
ASAL_CAVITY-LEVEL_IVHemorrhage											X	
Submucosal Pigment Depositions - Serous Exudate	n											· · · · · · · · · · · · · · · · · · ·
MPH NODE, TRACHEOBRONCHIAL Hyperplasia of Foamy		1	- X			. X	X	, X	. X	 X	X	
Macrophages				1	1	-	•	•				
Lymphoid Hyperplasia Pigment Deposition Hemorrhage		1		1	1				-			
nemorrhage h: DNEY				-					·			
Regenerative Tubular La Epithelium Casts	-		. 1	-	1	1	1		, 1		, 1	
EPL		I		1	_ <u>-</u> I-1	4			· <u></u>			
Experimental Pathology Laborat	ories	Inc		K	еу		in, ma	H	2 ·	5 an	section it mplete	n A = Aut (yks) (X = N + Bernul + 30) 3 = M, denate (4 = M, denato) Sevi c Section

1

RZ-75 90 Day Sacrifice Male Rats						Gr	oup	N													
	A N U I M B A E L R	3 7 3 - 0 9	3 7 3 3 - 0 1 0	3 7 3 3 - 0 1	3 7 3 3 - 0 1 2	3 7 3 3 - 0 1 3	3 7 3 3 - 0 1 4	3 7 3 3 - 0 1 5	3 7 3 3 - 0 1 6	3 7 3 3 - 0 1 7	3 7 3 3 - 0 1 8										
KIDNEY (CONTINUED)																					
Cortical Infarct						_	_							-			-	-	•	-	-
Foci of Mononuclear Cells		1										_		,	-	-				-	
Pigment Deposition		1	1	1_	1	1	1	1	1	1	1		.	-						-	-
LIVER		X	X	X	X		X	 	<u> </u>	X_	X	 			-				<u>-</u>	-	. <u>.</u> .
Bile Duct Hyperplasia				_		_			_	-	_	_		•							
Foci of Mononuclear Cells		l				1		1													
Cholangiofibrosis											• • •		- "					_		-	_
Pigment Deposition			•	•	-			•				•	•	•		•		-			
						•		•	-	•	-		•	·	•	•				•	
]		-	_		•				-	•			-		-	-	-		-
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		1	-																		
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		-	-						-												
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L		<u> </u>																			

11-15

Experimental Pathology Laboratories, Inc.

EPL

Key P + Present 1 - Minima:

N = No Section
2 = Sight
1 = 300 aproveds

A = 4, this x = 10 th Remarkable 3 = Milderate y Seven

GROUP	DOSE (mg/m3)	TREATMENT
L	0	Controls
M	1	Low Exposure Concentration
N	10	Medium Exposure Concentration
0	100	High Exposure Concentration

12.

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v.

F

•

100mm 100mm

ċ

RZ-75	
90 Day	Sacrifice
Female	Rats

Group L

	A P	3 7 3 1 - 5 0	3 7 3 1 - 5 1	3 7 3 1 - 5 1	3 7 3 1 - 5 1	3 7 3 1 - 5 1	3 7 3 1 - 5	3 7 3 1 - 5 1	3 7 3 1 -5 1	3 7 3 1 5	3 7 3 1 - 5			
LUNG		+3					X				X			-31
Accumulations of Foamy										- •				Ī
Macrophages														7
Hyperplasia of Type II Cells	 S	- 1												ľ
Pigment Deposition														
Adhesion		7			. –				-					
Hemorrhage		- 1												_] _],
Peribronchial Lymphoid]					, -							```\ ``
<u>Hyperplasia</u>		1_	1	. 1.	_ 1_	1		2	. 1	1				
NASA) CAVITY (EVEL I						 M	v				-			-
NASAL CAVITY-LEVEL I		- 1												<u> </u>
Hemorrhage														
Submucosal Pigment Deposition Congestion													•	
Company E. A.A.		1						٠.						
Foreign Material		- 1						• •	-	-				
Nonsuppurative Rhinitis		- 1					• • •	-	-	•	• -			
Cystic Glands		1 -		-	-	-	-	•	-	•		• • • •	•	1
		1	-		-				-			• • • •	-	
NASAL CAVITY-LEVEL II	-	X		X	X	N	, X	X	· X	X	٠			
Hemorrhage	-			. "		••	<i>,</i> "'	•	,,					1,1
_Submucosal Pigment Deposition		1		-	•		•					•		-
Inflammation of Nasolacrima						•		•	•					
Duct	-		2		•	•	•							
Foreign Body	_		-					-						
Focal Squamous Metaplasia	-	1	•	•	-	•	-					•		
Focal Inflammation		1		_		•	,			•		-		

11-16

EPL Experimental Pathology Laboratories, Inc.

P+Present N+No Section
1+Mnma 2 Sight
5+Severe High I - Pricomplete Section

RZ-75 90 Day Sacrifice Female Rats	<u></u>				Gr	oup	. L				-							
1 T	U 3	3 7 3 1	3 7 3 1	3 7 3 1	3 7 3 1		3 7 3 1	3 7 3 1	3 7 3 1	3 7 3 1								
A L	E - 5 0 9	5 1 0	5 1 1	5 1 2	5 1 3	5 1 4	5 1 5	5 1 6	5 1 7	5 1 8								
WASAL CAVITY-LEVEL II (CONTINUED)		<u> </u>															
Congestion	j			-	-				•	3		•		•	•			
Serous Exudate		•		-	•	•				3		-			-	•	-	
Nonsuppurative Rhinitis				•	•	-		-	•		•				•			
Cystic Glands			_	-	,		•		•			-			-			
+				•	-	•			-	-	-			-	•	•	-	
NASAL CAVITY-LEVEL III	X	X	X	χ	N	X	X	X	X			•		•			•	
Hemorrhage		•	•		-				-			•		-	•			
Submucosal Pigment Deposition			-				-	-		•				-	•	-		
Serous Exudate	} -	· ·	-			•				1		٠						
NASAL CAVITY-LEVEL IV Hemorrhage	_ X	. X	X	X	N	X	X	X	X	•					-			•
Submucosal Pigment Deposition		•		•		-			•		•			-				
Serous Exudate	1	-		-				-	-	1					•			
YMPH NODE, TRACHEOBRONCHIAL	X	-	. X	X	X	X	N	N	N	N			•		-			
Hyperplasia of Foamy	+		-															
Macrophages																		
Lymphoid Hyperplasia		. 2																
Pigment Deposition		-																
Hemorrhage																		
</td <td></td> <td>v</td> <td>¥</td> <td></td> <td>٧</td> <td></td> <td>X</td> <td></td> <td>¥</td> <td>X</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>		v	¥		٧		X		¥	X								
Regenerative Tubular	1	. ^	X		X		۸		۸	٨								
·	1	÷	•															
Casts	1	•	•		•													
:																		

11-17

EPL Experimental Pathology Laboratories, Inc Key P = Present N = No Section A = Agroys S > = No Section 3 = Moderate 4 = Mills and the Experimental Pathology Laboratories, Inc S = Severimental 1 = Incidence eter Section

RZ-75 90 Day Sacrifice Female Rats			-			. Gr	oup	L														
	A N U I M B A E L R	3 7 3 1 - 5 0 9	3 7 3 1 - 5 1 0	3 7 3 1 - 5 1	3 7 3 1 - 5 1 2	3 7 3 1 - 5 1 3	3 7 3 1 - 5 1 4	3 7 3 1 - 5 1 5	3 7 3 1 5 1 6	3 7 3 1 - 5 1 7	3 7 3 1 - 5 1 8											
KIDNEY (CONTINUED)										<u>-</u> _												→ `
<u>Cortical Infarct</u>		1															. •					,
Foci of Mononuclear Cells									. 1					•								نم م
Pigment Deposition		1_			. 1	-	. 1		·												_	
		ļ _					-	<u>.</u> .	-		-		٠.	-	,						-	·
LIVER	·	X.	_ X _	, X	_ X	X	, X	X	, X	, X	X	-		_								Ī
<u>Bile Duct Hyperplasia</u>		ļ		-		-	-												-	-		i
Foci of Mononuclear Cells		1										-	-		-				-	-	<u>-</u> -	
Cholangiofibrosis	- · · · - ·	\ 			-																-	į.
Pigment Deposition									-		-		-			-		÷				
BRAIN		_ X	X	X	X	N	X	X	X	Χ	X		-		•		-				•	;
PITUITARY		1	. N		X	N	X	. X	, X	X	, X	•	-	÷	-		-		-			.]
ADRENAL		1	 _ X	 Y	 X	X	X	¥	X	 X	X											
Hemorrhage			. ''	. "	. ~	•	,			,	- :`			٠							٠	
Vacuolated Cortical Cells			-						•	*												
			· 																			
EYE	_	X	X	_ X	X	N																
Corneal Subepithelial																						ļ
Basophilia																						Ì
THYGOID		X	_ X	X	X	X	X	X	X	X	X		٠									
	_		_							_			٠									

11-18

Experimental Pathology Laboratories, Inc.

Key P Present N = No Section

† Minima 2 = Sight

5 Silvere man 1 = incomplete Section

A Autority No. 3 + 1, 1 Remarkst = 3 + Moderate = 4 + Moderate v Seve

Z-75 O Day Sacrifice Female Rats						Gr	oup	L											 		
	A N U I M B A E L R	3 7 3 1 - 5 0 9	3 7 3 1 - 5 1 0	3 7 3 1 5 1	3 7 3 1 - 5 1 2	3 7 3 1 - 5 1 3	3 7 3 1 - 5 1 4	3 7 3 1 - 5 1 5	3 7 3 1 - 5 1 6	3 7 3 1 -5 1 7	3 7 3 1 5 1 8										
ARYNX		X	X	X	_ X	X	X	X	X	X	Х								 		
Foci of Mononuclear Cells					-															-	
NACUEA		-					-					-	- -		. 	-					
Hemorrhage		X	. X	Х	_ X	. Х	X	. X	Х	, X	. X				-						•
. Trompy ringg						•	-	•	~				-	•				-		٠	
HEART	~	X	X	X	X	X	X		X	X	X		-		-		-	=		÷	=
Nonsuppurative Myocarditis]		-			- .	1			-	-				-		•			
Pigment Deposition				-									-								•
SPLEEN		X	, _ X	_ X	_ X	X	_ X	X	X	X	X		•					-			
ANCREAS		X	_ X	X	X	X	X	X	X	X	X										
					-							_									
MPH NODE, POPLITEAL		X	_ X	X	N	X	. X	N	N	. X	X										
TOMACH		x	. X	X	X	X	X	X	X	X	X	-	-		٠						
JODENUM		x	X	X	X	X	X	X	X	X	X										
CUM		X	-	X	X				X	X	X										
Nematodiasis			P			Ρ	P	P					•								
DLON		X	X		X	X	X	X		X	X										
Nematodiasis				P		•	,,		P	, -	,,				٠						
					•		·								•						
		<u></u>																	 		

11-19

Experimental Pathology Laboratories, Inc

N N Section 2 - Supr

90 Day Sacrifice Female Rats						Gr	oup) L										 	2
A N I N A L	U I	3 7 3 1 -5 0 9	3 7 3 1 - 5 1 0	3 7 3 1 - 5 1	3 7 3 1 - 5 1 2	3 7 3 1 - 5 1 3	3 7 3 1 - 5 1 4	3 7 3 1 - 5 1 5	3 7 3 1 - 5 1 6	3 7 3 1 - 5 1 7	3 7 3 1 - 5 1 8								
SKIN		X	X	X	X	X	X			X									Ė
OVARY		X	Ņ	X	 _ ,X	- _ X	X	 _ X	. , , , , , , , , , , , , , , , , , , ,	_ _ X _	_ X			_			-	-	
UTERUS Dilatation		-								X					-	-	-		
URINARY BLADDER		X		. X		X		X		N	X		-		 			- .	-
FEMUR		I			X		X	X	X	X	X	-						•	į
	·		 -	-		-	-		-					-					
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>42-75 >30 Day Sacrifice Female Rats						Gr	oup.	0											
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UNG																			
Accumulations of Foamy								_					•	_			-	•	
<u>Macrophages</u>		3	2	2	2	3	3	2	2	_2	3				_		•		
Hyperplasia of Type II Cells		3	3	3	2	3_	3	2	2	2	3				•				
Pigment Deposition		1_	1	1	1	1	1	1	1	1	1		_	_					
Adhesion		_																·	
Hemorrhage													•			,		•	
Peribronchial Lymphoid								•	•	•			•		-	•			
Hyperplasia		2	1	2	1	2	1	2	1	1	1								
WASAL CAVITY-LEVEL I		X	X		X		X		X		X			٠				-	
Hemorrhage				_	_		•		•	-				-					-
Submucosal Pigment Deposition Congestion	<u>n</u>		- 	1		1		_ 1		1		-			-	•			
Serous Exudate					•			•		-	•					•			
Foreign Material			<u>-</u>	P					•			·							
Nonsuppurative Rhinitis	-	1					*				-	. –		٠	-				-
Cystic Glands		İ		-	•		-	•		•		٠		•					
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NASAL CAVITY-LEVEL II Hemorrhage				-	-									-					
Submucosal Pigment Depositio	n .	2	. 2	. 2	. 2	2	2	2	2	2	2								
Inflammation of N solacrimal		_	. -	. -		_			•	•									
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Foreign Body		-											-						
Focal Squamous Metaplasia Focal Inflammation			·	-			,												
					1 2														

11-21

EPL Experimental Pathology Laboratories, Inc.

-, 27-75

Key PH Present NH No Section A + 40th (45) | X + 10 th Grade + 0th e | 1 + Minimal | 2 + Singht | 3 + Moutourle | 4 + Minterprese | 5 + Stylene High | 1 + Incomplete Section

RZ-75 90 Day Sacrifice Female Rats	_				Gr	oup	0												 ,		
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NASAL CAVITY-LEVEL II (CONTINUED)	9	Ō	<u>i</u>	2	3	4	5	6	7	8				.							
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Nonsuppurative Rhinitis			-	-:					- · •	- -		•	-	- ·-	• •	-					-
Cystic Glands	1										-				-			-	•	_	 ن
NASAL CAVITY-LEVEL III											•		-	-		•	-	-	-	· -	
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NASAL_CAVITY-LEVEL_IV Hemorrhage				-										•							
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LYMPH NODE, TRACHEOBRONCHIAL	N.			-		-		-	-	N											
Hyperplasia of Foamy		•	•		-			•		••											- 1
Macrophages		2	3	1	3	2	2	2	2		-										
Lymphoid Hyperplasia	1	•	3	4			2	-													
Pigment Deposition		1	1	1	1	1	1	1	1												
Hemorrhage			-		-		Ī		-												
	1		•						•												j
KIDNEY	1	٠	•			-															
Regenerative Tubular	1	•											,								1
Epithelium	1	•	•																		
Casts		-	•									•		•							
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E P L Experimental Pathology Laboratories, Inc

ey P = Present N = N; Section 1 = Mn inst 2 = 5 ght

RZ-75 90 Day Sacrifice Female Rats						Gr	oup	0													
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TONEY / CONTINUED)	<u> </u>	9	0	1	2	3	4	5	6	7_	_8_										
Cortical Infarct		.		••	•	• •		•			•		• •	•	•	-	-	٠	•		
Foci of Mononuclear Cells		1	1	•			• .					•				•	-	-	-	٠	
Pigment Deposition			3	3	3	2	3	2	2	2	 3			-	-				•		
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TEIVER									-				-		_		•				
Bile Duct Hyperplasia					•			-													
Foci of Mononuclear Cells									-				-	.		_					
Cholangiofibrosis	- · · -	_																	-		
Pigment Deposition		1	_ 1	1	. 1	1	1	1	1	1	1							-			
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ADRENAL		$ _{\mathbf{x}}$	X	X	 X	X	. X	Х	X	X	. X										
Hemorrhage	-										- ''			•					•		
Vacuolated Cortical Cells	•			-					-					•							
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EYE			_ X	X	X	X	X	X	X	X	X										
Corneal Subepithelial																					
Basophilia																					
1,																					
HYROID		X	X	X	X	X	X	X	N	Á	X			•							
1																					
<u> </u>		<u> </u>																			

11-23

Experimental Pathology Laboratories, Inc.

Key P = Prevent N = No Section A = Authors X = Not fermalisate 1 = Minimar 2 = Sught 3 = Minimare 4 = Minimare 3 = Section 5 = Several High 1 = recomplete Section

RZ-75 90 Day Sacrifice Female Rats

Group 0

	A N N U I M	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4											
	M B A E L R	5 0 9	5 1 0	5 1 1	5 1 2	5 1 3	5 1 4	5 1 5	5 1 6	5 1 7	5 1 8											
LARYNX		X	X			X	X		<u> </u>	X		_	_									
Foci of Mononuclear Cells		_		_1	1	- ,				-	-				· · -				•			-
TRACHEA		X	X	 _ X _	X	_ X	_ X		X	_ X	X			• • -					•	· • · •		1
Hemorrhage		-		•			-		-				-	•	••			4	-		-	- - ! !
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Nonsuppurative Myocarditis_ Pigment Deposition		1	 									-		<u>.</u>								
SPLEEN		x	. X	_ X	, X	X	X	X	X	X	_ X		-				-				· <u>.</u> . <u>.</u>	
PANCREAS		X	. X	 . X .	- X	. X	X	X	X	X	X						-					
LYMPH NODE, POPLITEAL	. .	N	. X	X		 , X	 . X	X	. X	. X	. X	-		•								
STOMACH		X	, X	X	X	X	X	X	X	, X	X		-									
DUODENUM		x	X	X	X	X	X	X	χ	X	X											-
CECUM Nematodiasis	-	X	X	X	X	X	X	X	X	X	P											2
COLON Nematodiasis		X	, X	X	X	X	X	X	X	P	P											
			_																			

11-24

Experimental Pathology Laboratories, Inc.

Key P+ Present N= No Section
1 = Mormal 2 = Sight
5 = Severic High | 1 = incomplete Section

A = Audosysis - Die Notherberahabte 3 = Moderate - 4 = Moderate's Seventi High

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	A N N U I M M B	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4									
	A E L R	5 0 9	5 1 0	5 1 1	5 1 2	5 1 3	5 1 4	5 1 5	5 1 6	5 1 7	5 1 8									
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UTERUS Dilatation		X_	X	X	X	X	 2	_ X	X	_ X	. X		-	·	•	•				·
RINARY BLADDER		X	X		X	. X	 	. X	 _ X	. X	X_	 -			_	-				
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11-25

EPL Experimental Pathology Laboratories, Inc.

RZ-75 Group M 90 Day Sacrifice Female Rats 3 3 3 3 1 1 1 1 1 1 1 _____X_X_X_X LUNG Accumulations of Foamy Macrophages _____ Hyperplasia of Type II Cells Pigment Deposition Adhesion Hemorrhage Peribronchial Lymphoid Hyperplasia 1 1 1 1 1 1 _____ NASAL CAVITY-LEVEL I X X X X X X X X X X _Hemorrhage_____ Submucosal Pigment Deposition _Serous_Exudate_____ Foreign Material Nonsuppurative Rhinitis _Cystic Glands NASAL CAVITY-LEVEL II _Hemorrhage Submucosal Pigment Deposition Inflammation of Nasolacrimal Duct Foreign Body Focal Squamous Metaplasia Focal Inflammation

11-26

Experimental Pathology Laboratories, Inc.

Key P + Present N + No Section
1 + Min ma 2 + 5 cht
5 + Severe High 1 + mot markete Set

					Gr	oup	M											
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	N 7 U 3 M 2	7 3 2		3 7 3 2					7 3 2	7 3 2								
	E 5 0 9	5 1 0	5 1 1	5 1 2	5 1 3	5 1 4	5 1 5	5 1 6	5 1 7	5 1 8								
ASAL CAVITY-LEVEL II (CONTINUED)																	
Congestion							-		.					~-				
Serous Exudate						.				_								
Nonsuppurative Rhinitis										_					.			
Cystic Glands										. . .	-		_					
i				-• ·	_			·			-				. <u>-</u>	-		
NASAL CAVITY-LEVEL III	$\int X$	X	X	X	X	X	X	_ X _	χ	_ X			-~				-	
Hemorrhage		<u>-</u>					_						-					
Submucosal Pigment Deposition	_]_		_					_					_					
Serous Exudate		·-···		-										-			* -	
JASAL CAVITY-LEVEL IV	N	N	 N	 X	N	N	X	X	 X	X			-		. . .	-	*	
Hemorrhage	- -		•			•		-		•				•				- '
Submucosal Pigment Deposition			•		-	•				•			•	•	-	-	•	
Serous Exudate		-			=	•	•							-			*	- \ -
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YMPH NODE, TRACHEOBRONCHIAL	x	 X	N	X	X	- N	χ	N	N	X		•	•	-				- 1
Hyperplasia of Foamy		-	- "					•		•				•				
Macrophages	• • •		-	•	•		•	•		•								
Lymphoid Hyperplasia	•	-	•	•					-		• •							
Pigment Deposition	-	-	-	•		~		•		•		•						
+ Hemorrhage		•	-			•												
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1. IVER	X	X	•			X			X	X	•							
Bile Duct Hyperplasia	1	- ''	1	•				•	••	••								
Foci of Mononuclear Cells		-	1			•	1	1			•		-					•
Cholangiofibrosis		•	. •	. •	•	•	. •	•		•	•	•	•					
文			•	11-2	27													

Key P = Present N = No Section
1 Minima 2 = Sight
5 = Severe High 1 = Incomplete Section

A = Aprovision - X = Not Remarkable 3 = Moderate - 4 = Moderates, Severe High

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Experimental Pathology Laboratories, Inc.

RZ-75 90 Day Sacrifice Female Rats	!	_				Gr	oup	M	_												
	A N N U I M M B A E L R	3 7 3 2 - 5 0 9	3 7 3 2 - 5 1 0	3 7 3 2 - 5 1	3 7 3 2 - 5 1 2	3 7 3 2 - 5 1 3	3 7 3 2 - 5 1 4	3 7 3 2 - 5 1 5	3 7 3 2 - 5 1 6	3 7 3 2 - 5 1 7	3 7 3 2 - 5 1 8										
LIVER (CONTINUED)										_				-			-				_
Pigment Deposition						-					- · -		· · ,	,							
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EPL Experimental Pathology Laboratories, Inc.

Z-75 90 Day Sacrifice Temale Rats						Gr	oup	N											 	7
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ZUNG					_				X	X	-			-		-		-		
Accumulations of Foamy	-	_			. -				_	-	_		-	-		~.			 	.
Macrophages		1	1	.	1	. <u>.</u>	-	-	<u>-</u>		. .				_		-		 - .	
Hyperplasia of Type II Cells			. 1										٠.	-	-				 	-
Pigment Deposition		1	. 1		_ 1_	-	-			-		-			-	÷	-			.
Adhesion		-		-			-		•				-			-			-	1
Hemorrhage	-						-													-
Peribronchial Lymphoid														-						-
. Hyperplasia		1		. 1	. 1	1	1	1			1								- -	-
NASAL CAVITY-LEVEL I				 V	Y	v	. 🗸	V	V	Y	¥						-			1
Hemorrhage		1	. ^	^	.^	^	. ^	- ^	. X	^	X									1
Submucosal Pigment Deposition	 .m	-		• •	•	-	-										-		•	1
Congestion	,,,,		-						•				•						 -	
Serous Exudate	-			•	-			-		-	•	-			-					
: Foreign Material			•						•											1
Nonsuppurative Rhinitis		1	-			-			-											
Cystic Glands				•																
				•	-	-			•	•										1
NASAL CAVITY-LEVEL II		Y	Y	Y	¥	¥	Y	¥	X	N	¥									
- Hemorrhage		^	, ^	^	. ^	^,	^	^	•	.,	^									1
Submucosal Pigment Deposition	ממ																			
Inflammation of Nasolacrimal		ţ	•																	
Duct			•	•																
Foreign Body		1	•																	
Focal Squamous Metaplasia		1	•			-		•												
Focal Inflammation				•	•															
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11-29

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Key P = Present N = N = Sh, tion A = Authorises 3 = N = N = Remorkable 1 = Minima 2 = Stight 3 = N = D ate 4 = N = D ate 3 = N = D ate 3 = N = D ate 3 = N = D ate 3 = N = D ate 3 = N = D ate 3 = N = D ate 3 = N = D ate 3 = N = D ate 3 = N = D ate 3 = N = D ate 3 = N = D ate 3 = N = D ate 3 = N = D ate 3 = N = D ate 3 = N = D ate 3 = D

RZ-75 90 Day Sacrifice Female Rats	_				Gr	oup	N N					 			•	 		
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NASAL CAVITY-LEVEL II (CONTINUED)												 		-				2.3
Congestion	- .	-	-													 	· • .	1
Serous Exudate							_		-	_		 				 		
Nonsuppurative Rhinitis		_												-				т,
Cystic Glands											-	-						
NACAL CAVITY LEVEL 111										-						 		. }
NASAL CAVITY-LEVEL III													-			 		
Hemorrhage Submucosal Pigment Deposition		 1				-					•		-					-{-
Serous Exudate							•			. •								
NASAL_CAYITY-LEVEL_IV_ Hemorrhage	X	_ X	N									•	-				-	1
Submucosal_Pigment Deposition	1								1									
Serous Exudate	1							•					•					
LYMPH_NODE, TRACHEOBRONCHIAL	X	. X		N	, X		. N	, X	÷	•								
Hyperplasia of FoamyMacrophages		-	. 1							1								
Lymphoid_Hyperplasia		. .																
Pigment Deposition		_	. 1							1								
_ Hemorrhage	-					1			2									-
KIDNEY	1	-	Y	X														
Regenerative Tubular		•	^	^								•						-
Epithelium		•										•						
Casts			•	-						·]
				7 2								 						_

11-30

Experimental Pathology Laboratories, Inc

Key Palesent Name Section
1 - Monaya 2 - Sight
5 - Section 1 - Monaya 1 - Sight

Z-75 90 Day Sacrifice Female Rats	Group N											
	A N U I M M B A E L R	3 7 3 3 - 5 0 9	3 7 3 3 - 5 1 0	3 7 3 3 - 5 1	3 7 3 3 - 5 1 2	3 7 3 3 - 5 1 3	3 7 3 3 - 5 1 4	3 7 3 3 - 5 1 5	3 7 3 3 - 5 1 6	3 7 3 3 - 5 1 7	3 7 3 3 5 1 8	
IDNEY (CONTINUED)								. . .		-		
Cortical Infarct			. –		. ~							
Foci of Mononuclear Cells Pigment Deposition		1	<u>.</u>			. <u>.</u> .	 1	1	<u>-</u>	- 1	- 1	
riginent beposition						. •			- · • - ·	•	:	·
EI VER			χ	χ.			χ				X	
. Bile Duct Hyperplasia						1	•	-		•		
Foci of Mononuclear Cells				·	1			1	1	1		
Cholangiofibrosis			.		-						-	
Pigment Deposition		1			-	, 1						
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11-31

Experimental Pathology Laboratories, Inc.

Key P = Present N = No Section
1 = Minima 2 = Sight
5 = Severe High | T = Incomplete Section

A + Autoysis — x + Not Remarkatie 3 + Moderate — 4 — Moderate v Severe High NINETY-DAY SACRIFICE

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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species Rats

Sex Males

Group Number 0 - Sacrificed

Dosage Level 100 mg/m³

及

727

| 大大田 | 東京 | 大大田 | 大大田 | 大大田 | 大田 | 大大田 | 大田 |

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Group Number 0 - Sacrificed

Males

Sex

Species Rats

.

Dosage Level 100 mg/m³

Microscopic Observations	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding lesion Hyperplasia of foamy macrophages; lymphoid hyperplasia; pigment deposition	Accumulations of foamy macrophages; s hyperplasia of type II cells; pigment deposition	No corresponding lesion (adipose tissue)		Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition		No corresponding lesion (adipose tissue)	No corresponding lesion (adinose	tissue)tissue
Chent's Gross Observations	Diffuse mild-moderate dye deposition	Green Dark greenish brown color	Dark greenish brown mottling in all lobes	Green	Green	Dark_and enlarged 2x	Diffuse moderate dye deposition	Green contents	Green	Green hair	Green tinted
Client's Tissue Identification	Lung	Skin Tracheobronchial lymph node	Lung	Fatty tissue	Skin	Tracheobronchial lymph node	Lung	Stomach	All body fat	Skin	Fat tissue
Animal Number	3734-011 (Cont'd)	3734-012			3734-013					3734-014 Skin	

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Section From

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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species Rats

Sex Males

Group Number 0 - Sacrificed

Dosage Level 100 mg/m³

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Microscopic Observations	Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding leston Lymphoid hyperplasia; pigment deposition	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding lesion (adipose tissue)	No corresponding lesion Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposi-	tion Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding lesion (adipose tissue)	Atrophy Arophy
:	Dark brown	Mottled brownish green areas	Dark green		Greenish color	Green hair Dark brown	_	Green tinted	Small watery
 - 		Lung	Skin Skin Tracheobronchial lymph node		Fat	SkinTracheobronchial lymph node	Lung	Fat tissue	Skin
Animal Number	3734-014 (Cont'd)		3734-015			3734-016 Skin			3/34-01/

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Group Number 0 - Sacrificed Males Sex Species Rats

Dosage Level: 100 mg/m³

Microscopic Observations	Hyperplasia of foamy macrophages; lymphoid hyperplasia; pigment deposition	Accumulations of foamy macrophages; n hyperplasia of type II cells; pigment	No corresponding lesion (adipose tissue)	No corresponding lesion	Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition	Accumulations of foamy macrophages; n hyperplasia of type II cells; pigment deposition	No corresponding lesion	No corresponding lesion (adipose tissue)		
Client's Gross Observations	Dark brown	Dark green and brown speckled pattern	Discolored	Green	Dark and enlarged 3x	Diffuse mild-moderate dye deposition	Green contents	Green		
Client's Tissue Identification	Tracheobronchial lymph node	Lung	Ta t	Skin	Tracheobronchial lymph node	Lung	Stomach	All body fat		
An:mal Number	3734-017 (Cont'd)			3734-018						

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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

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Group Number M - Sacrificed Sex Males Species Rats

Dosage Level 1 mg/m³

		,—	 	 	 	 	 	 	
Microscopic Observations	No section								
Client's Gross Observations	Congested, reddened								
Chent's Tissue Identification	Tracheobrenchia! lymph node								
Animal Number	3732-014								

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Dosage Level 10 mg/m³	Microscopic Observations	No_corresponding lesion	Pigment deposition	No corresponding leston	No corresponding leston	No corresponding lesion	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding leston Accumulations of foamy macrophages;	pigment deposition	No corresponding lesion	No corresponding lesion			
Group Number N - Sacrificed	Client's Gross Observations	Mottled brownish green areas	Grayish_tint_to_all_lobes	Brown ish green color	Green/gray_tint_to_all_lobes	Mottled brown areas	Mottled brownish discoloration	Brown mottled discoloration	Greenish tint to all lobes	Greenish brown mottled discoloration	Mottled brownish green discoloration			
Sex: Males	Client's Tissue Identification	Lung		Lung	Lung	Lung	Lung		Lung	Lung	Lung			
Species Rats	Animai	3733-009	3733-010 Lung	3733-011 Lung	3733-012 Lung	3733-013	3733-014	3733-015	3733-016 Lung	3733-017	3733-018			

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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

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Microscopic Observations Dosage Level. 0 mg/m³ Adhesion Client's Gross Observations Left lobe adhered to rib cage L - Sacrificed Group Number Femaies Client's Tissue Identification Sex Lung Rats 3731-511 Animat Number Species

Sacrifice RZ-75 90 Day

CCRRELATION OF GROSS AND MICROSCOPIC FINDINGS

Group Number

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Rats

Species

Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposi-Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposi-Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposifeamy macrophages; foamy macrophages; Accumulations of foamy macrophages; No corresponding lesion (adipose No corresponding lesion (adipose hyperplasia of type II cells: hyperplasia of type II cells; hyperplasia of type II cells: Microscopic Observations No corresponding lesion No corresponding lesion pigment deposition pigment deposition pigment deposition Dosage Level. 100 mg/m³ Accumulations of Accumulations of No_section tissue) tissue) tion Heavy dye deposition in all lobes Client's Gross Observations Mottled brownish green areas 0 - Sacrificed Greenish discoloration Mottled brownish green Dark_and_enlarged_2x Green tinted Dark brown Dark brown Green hair Dark brown Green Tracheobronchial lymph node fracheobronchial lymph node 3734-510 Tracheobronchial lymph node 3734-512 Iracheobronchial lymph node Client's Tissue Identification **Females** Fatty tissues Fat tissue Skin Skin Lung Lung Lung 3734-509 3734-511 Animal Number

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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

- Sacrificed

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Group Number

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 100 mg/m^3

Dosage Level

foamy macrophages; pigment deposi-tion Lymphoid hyperplasia; hyperplasia of foamy_macrophages;_pigment_deposi-Lymphoid hyperplasfa; hyperplasfa of Accumulations of foamy macrophages; Accumulations of foamy macrophages; Accumulations of foamy macrophages; No corresponding lesion (adipose hyperplasia of type II cells; pigment deposition hyperplasia of type II cells; hyperplasia of type II cells; Microscopic Observations No corresponding lesion No corresponding leston No corresponding lesion pigment deposition pigment deposition tissue) tion dye deposition Diffuse mild-moderate dye deposition Client's Gross Observations Heavy_speckled_pattern of Greenish brown color Green contents Dark brown Dark brown Green Green Green Green Tracheobrunchial lymph_node Tracheobronchial lymph node Client's Tissue Iden(ification Females Sex All body fat Stomach Skin Skin Lund 222 Skin Lung Rats 3734-514 3734-513 3734-512 (Cont'd) Anımal Number Species

Green_hair_

Green

tissue

Fatty

Skin

_ 3734-515

No corresponding lesion (adipose

tissue)

_No_corresponding_lesion_

RZ-75
90 Day Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species Rats
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Dosage Level 100 mg/m³

Microscopic Observations	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding lesion (adipose tissue)	No_corresponding leston Lymphoid hyperplasia; hyperplasia of	tion tion	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding lesion	No corresponding lesion (adipose tissue)	No corresponding leston	Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding lesion (adipose tissue)	No corresponding lesion	
Client's Gross Observations	Mottled brown areas	Green tinted	eer	Dark and enlarged 2x	Diffuse dye deposition, mild-moderate	Green contents	Green	Dark green	Brownish green color	Dark brownish green color	Green color	Green	See 277-102 Sec 1777
Client's Tissue Identification	Lung	Fatty tissue	!	Tracheobronchial lymph_node	Lung	Stomach	All body fat	Skin	Tracheobronchial lymph node	Lung	Fatty tissue		
Anımal Number	3734-515 (Cont'd)		3734-516					3734-517			; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ;	3734-518 Skin	

RZ-75 90 Day Sacrifice

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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

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Species Ra	Rats Sex Females (Group Number 0 - Sacrificed	Dosage Level 100 mg/m
Animal	Client's Tissue Identification	Client's Gross Observations	Microscopic Observations
3734-518 (Cont'd)	Tracheobronchial lymph_node	irk_and_enlar	No_section
	Stomach	Green contents	No corresponding leston No corresponding leston (adipose
	All body_fat	Green .	
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RZ-75 90 Day Sacrifice

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Microscopic Observations Dosage Level 1 mg/m³ No section Client's Gross Observations Group Number M - Sacrificed Congested 3732-511 Tracheobronchial lymph node Client's Tissue Identification Females Sex Rats Animal Number Species

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Rĩ-75 90 Day Sacrifice

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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species Rats

Sex Females

Group Number N - Sacrificed

Dosage Level 10 mg/m³

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Animal	Client's Tissue Ideniification	Client's Gross Observations	Microscopic Observations
3733-510 Lung	6	Diffused brownish color with heavy green dye deposition Gray/green tint to all lobes, some con- centrated foci_scattered_on_all_lobes	Accumulations of foamy macrophages; pigment deposition Accumulations of foamy macrophages; pigment deposition; hyperplasia of type II cells
3733-511 Lung	9	Mottled brown areas Shows a diffuse brownish color with heavy focal dye deposition	No corresponding lesion Accumulations of foamy macrophages; pigment deposition
3733-513 Lung	6	Stuck to rib cage, mottled brown areas_Gray/green_tint to all lobes	No corresponding lesion No corresponding lesion
3733-515 Lung	9	Dull brown color	No corresponding leston
3733 <u>-</u> 516, tung 3733-517 <u>, L</u> ung	<u></u>	Diffuse green tint to all lobes Green/gray tint to all lobes, some more marked concentration in scattered areas of all lobes	No corresponding lesion No corresponding lesion
3733-518Lung	<u>6</u>	Mottled brown discoloration	No corresponding lesion

THIRTY-DAY SACRIFICE
SUMMARY INCIDENCE TABLES

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RZ-75 30 Day Sacrifice Male Rats

	Group L	Group O	Group M	Group N	
NASAL CAVITY-LEVEL IV					
(NO. EXAMINED)	(10)	(10)	(10)	(9)	
Submucosal Pigment Deposition		10		2	
Hemorrhage			1		
LYMPH NODE, TRACHEOBRONCHIAL					
(NO. EXAMINED)	(7)	(10)		(8)	
Lymphoid Hyperplasia		10		1	
Hyperplasia of Foamy					
Macrophages		10			
Pigment Deposition		10			
Нетоггнаде					
KIDNEY (NO. EXAMINED)	(10)	(10)		(10)	
Regenerative Tubular					
Epithelium	6	6		5	
Foci of Mononuclear Cells	3	4		2	
Casts	1	5		3	
Pigment Deposition	10	10		10	
Tubular Mineralization		1			
LIVER (NO. EXAMINED)	(10)	(10)		(10)	
Foci of Mononuclear Cells	3	3		6	~ "
Bile Duct Hyperplasia	1	1		1	·
Focal Capsular Fibrosis	1	- · · ·			
Pigment Deposition		10			
Hernia			_		
	· · · · · · · · · · · · · · · · · ·	• —	* ***		
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RZ-75 30 Day Sacrifice Male Rats

	Group	Group O	Group M	Group N		
BRAIN (NO. EXAMINED)	(10)	(10)				
PITUITARY (NO. EXAMINED)	(10)	(10)				
ADRENAL (NO. EXAMINED)	(9)	(10)				
▼ Vacuolated Cortical Cells	5	4				
EYE (NO. EXAMINED)	(10)	(10)				
THYROID (NO. EXAMINED)	(10)	(10)				
LARYNX (NO. EXAMINED)	(10)	(10)				
Foci of Mononuclear Cells		6		<u></u> .		
TRACHEA (NO. EXAMINED) Foci of Mononuclear Cells	(10)	(10)				
FOCT OF MONORIDE PEAR CETTS						 !
HEART (NO. EXAMINED)	(10)	(10)				
Nonsuppurative Myocarditis	7	22				
Interstitial Fibrosis	2	2				
SPLEEN (NO. EXAMINED)	(10)	(10)				
PANCREAS (NO. EXAMINED)	(10)	(10)			. <u></u> .	
LYMPH NODE, POPLITEAL						
(NO. EXAMINED)	(10)	(9)	·· -	→ · · · · · · · · · · ·	• • •	
Pigment Deposition	1	2				- •
Lymphoid Hyperplasia	1	1				

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RZ-75 30 Day Sacrifice Male Rats

	Group	Group O	- Group M	Group N		Ó
STOMACH (NO. EXAMINED)	(10)	(10)				Į
DUODENUM (NO. EXAMINED)	(10)	(10)				
CECUM (NO. EXAMINED)	(10)	(10)				. i
Nematodiasis	3	1				
COLON (NO. EXAMINED)	(10)	(10)				1
Nematodiasi	1	1				-
SKIN (NO. EXAMINED)	(10)	(10)				•
TESTIS (NO. EXAMINED)	(10)	(10)				Ì
EPIDIDYMIS (NO. EXAMINED)	(10)	(10)				
PROSTATE (NO. EXAMINED)	(10)	(10)				
URINARY BLADDER (NO. EXAMINED)	(10)	(10)				+
FEMUR (NO. EXAMINED)	(9)	(10)			· · · · · · · · · · · · · · · · · ·	
ADIPOSE TISSUE (NO. EXAMINED)		(10)			- 	1
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RZ-75
30 Day Sacrifice
Female Rats

	Group L	Group O	Group M	Group N			
LUNG (NO. EXAMINED)	(9)	(10)	(10)	(10)			
Accumulations of Foamy							
Macrophages		10		2			
Hyperplasia of Type II Cells		10		1			
Pigment Deposition		10		2			
- Hemorrhage			1				
Edema							
Congestion			2				
Peribronchial Lymphoid			<u> </u>				
Hyperplasia	5	10	5	10	. . — — —	· ·	
NASAL CAVITY-LEVEL I							
(NO. EXAMINED)	(9)	(9)	(10)	(10)			
Hemorrhage					·		
· Submucosal Pigment Deposition		5	·			· · · · · · · · · · · · · · · · · ·	
Cystic Glands							
- NASAL CAVITY-LEVEL II							
(NO. EXAMINED)	(9)	(9)	(10)	(10)	··		
Hemorrhage						·	
Submucosal Pigment Deposition		9		1			
Serous Exudate						••	•
Inflammation of Nasolacrimal							_
Duct	1	- - · · · ·					
·							
NASAL CAVITY-LEVEL III				· - · · · ·	•		
-(NO. EXAMINED)	(9)	(9)	(9)	(9)	-		
Submucosal Pigment Deposition		9		5	•		
Hemorrhage							

RZ-75 30 Day Sacrifice Female Rats

	Group L	Group 0	Group M	Group N		_
NASAL CAVITY-LEVEL IV						_
(NO. EXAMINED)	(9)	(9)	(10)	(10)		_
Submucosal Pigment Deposition		8		6		_
Hemorrhage						
LYMPH NODE, TRACHEOBRONCHIAL		 				
(NO. EXAMINED)	(7)	(10)		(9)		_
Lymphoid Hyperplasia		10				_
Hyperplasia of Foamy						
Macrophages		10				
Pigment Deposition		10				
Hemorrhage				1		
KIDNEY (NO. EXAMINED)	(9)	(10)		(10)	-	
Regenerative Tubular						
Epithelium		1		2		_
Foci of Mononuclear Cells		1		2		
Casts						
Pigment Deposition	9	10		7		
Tubular Mineralization						
LIVER (NO. EXAMINED)	(9)	(10)		(10)		
Foci of Mononuclear Cells	: 4	3	- · · ·	2		
Bile Duct Hyperplasia	1		-,	1		
Focal Capsular Fibrosis	<u> </u>	1		- · · ·		
Pigment Deposition	<u>.</u>	10			-	
Hernia	1	1	-		•	
		i 	-		-	
						

₹Z-75 30 Day Sacrifice —emale Rats

	Group L	Group O	Group M	Group N	
BRAIN (NO. EXAMINED)	(9)	(9)			
<u> </u>					
PITUITARY (NO. EXAMINED)	(9)	(9)		_	
V					
ADRENAL (NO. EXAMINED)	(9)	(10)			
- Vacuolated Cortical Cells					
· · · · · · · · · · · · · · · · · · ·					
LEYE (NO. EXAMINED)	(9)	(9)			
II					
THYROID (NO. EXAMINED)	(9)	(10)			
÷					
LARYNX (NO. EXAMINED)	(9)	(10)			
Foci of Mononuclear Cells	2			· · · · · · · · · · · · · · · · · · ·	
TRACHEA (NO. EXAMINED)	(9)	(10)			
Foci of Mononuclear Cells	1				
HEART (NO. EXAMINED)	(9)	(9)			
Nonsuppurative Myocarditis		1			
Interstitial Fibrosis		·			_
		·•··		,	
SPLEEN (NO. EXAMINED)	(9)	(10)			
<u></u>			. _		-
PANCREAS (NO. EXAMINED)	(9)	(10)		<u> </u>	
iq ¹		-			
LYMPH NODE, POPLITEAL					
(NO. EXAMINED)		(10)		•	
Pigment Deposition		· -	· - · - · ·		
Lymphoid Hyperplasia					

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RZ-75 30 Day Sacrifice Female Rats

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	Group L	Group O	Group M	Group N	
STOMACH (NO. EXAMINED)	(9)	(10)			
DUDGE HALL (NO EVANTUED)	(0)	(10)			
DUODENUM (NO. EXAMINED)	(9)	(10)			
CECUM (NO. EXAMINED)	(9)	(10)			
Nematodiasis		2			
COLON (NO. EXAMINED)	(9)	(10)			 -
Nematodiasis	2	2			
SKIN (NO. EXAMINED)	(6)	(10)			
OVARY (NO. EXAMINED)	(9)	(10)	-		
Parovarian Cyst	2	1			
UTERUS (NO. EXAMINED)	(9)	(10)			 •
Dilatation	2	2			
URINARY BLADDER (NO. EXAMINED)	(8)	(10)			
FEMUR (NO. EXAMINED)	(9)	(10)			
ADIPOSE TISSUE (NO. EXAMINED)		(9)			
					
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THIRTY-DAY SACRIFICE

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HISTOPATHOLOGY INCIDENCE TABLES

GROUP	DOSE (mg/m3)	TREATMENT
L M N O	0 1 10 100	Controls Low Exposure Concentration Medium Exposure Concentration High Exposure Concentration

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Z-75 30 Day Sacrifice Male Rats						Gr	oup	L				 			 		
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UNG			X					X				 			 		
Accumulations of Foamy			. <u>-</u> .		.						-						
Macrophages					_						-			-			
Hyperplasia of Type II Cells				-				-	-		-						
Pigment Deposition					-				-	•							
Hemorrhage			.	-										-			
<u>Edema</u>																	
Congestion													-				
Peribronchial Lymphoid											-						-
Hyperplasia		1	•	. 1	1	. 1	1		1	1	. 1						
ASAL CAVITY-LEVEL I Hemorrhage Submucosal Pigment Deposition Cystic Glands	า วท			. X	. X	X	X .	X	3	X	X	4					
ASAL CAVITY-LEVEL II Hemorrhage	· ··	[X	X	X	X	2	X	X						
Submucosal Pigment Deposition Serous Exudate Inflammation of Nasolacrimal Duct	on		-														
NASAL CAVITY-LEVEL III Submucosal Pigment Deposition Hemorrhage	on .	X	X	X -	X	X	X	X	X	X	X				 	 	

V-1

EPL Experimental Pathology Laboratories, Inc

PriPresent N = No Section
1 = Minima 2 = 5 ght
5 = Severe = ght 1 = incomplete 5

A - Apt. you - 3 + 5 164 me + 108 m 3 - Moderate - 4 + Moderate opening

					Gr	onb	L 														
ANUIMBAELR	3 7 3 1 - 0 1 9	3 7 3 1 - 0 2 0	3 7 3 1 0 2	3 7 3 1 - 0 2 2	3 7 3 1 - 0 2 3	3 7 3 1 - 0 2 4	3 7 3 1 - 0 2 5	3 7 3 1 - 0 2 6	3 7 3 1 - 0 2 7	3 1 - 0 2											
	X.	<u>X</u>	X	_ X	, X	X	X	Х	X	_ X	-					_					
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	N U I M B A E L R	N U 3 M B 1 A E O 1 9 X X I O n X	N U 3 3 3 M B 1 1 A E 0 0 0 1 2 9 0 X X X 1 0 n	N U 3 3 3 3 3 3 1 1 1 1 1 1 2 2 9 0 1 1	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	A N 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	A N 7 7 7 7 7 7 7 7 7 7 8 U 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	A N 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	A N 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	A N 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	A N 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	A N 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	A N 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	A N N T T T T T T T T T T T T T T T T T	A N 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 8 1 1 1 1	A N 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 8 1 1 1 1	A N 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 8 1	A N 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 8 1	A N N 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	A N N T T T T T T T T T T T T T T T T T

RZ -75

RZ-75 30 Day Sacrifice Male Rats						Gr	onb	L									 	
6 6	A N N U I M B A E	3 7 3 1	3 7 3 1	3 7 3 1	3 7 3 1	_	3 7 3 1	3 7 3 1	3 7 3 1	3 7 3 1	3 7 3 1							
• •	L R	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5	0 2 5	0 2 7	0 2 8							
BRAIN		X		X	X		X					-				-	 	
PITUITARY		X	_X	X	X	X_	X	X	X	X	X			 -		-		
ADRENAL Vacuolated Cortical Cells				X					X	1	- . 1		-					·
EYE		x	<u> </u>	 X .	X	 X	X	, X	X	X	x	-		-	-			
THYROID		X	X ,	X ,	X	X	X	X	X	X	X		-	-	•	-		
LARYNX Foci of Mononuclear Cells		X	X	X	X	X	X	X	X	X	X	-			,			
TRACHEA Foci of Mononuclear Cells		X	X	X .	X	X	 . X	X	X	X	X		F1 - 1		•			
HEARTNonsuppurative Myocarditis Interstitial Fibrosis	-··	1	, ,	1		X		1 1	1	1	1	•						
SPLEEN		X	, X	 X	X	X	. X	X	X	X	X							
PANCREAS		X	X	X	X	X	X	X	X	X	X							

V-1

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EPL

Key P = Prevent N = No Section 1 = N' o mai 2 in 5 gint 5 = Severe might 1 = incomplete Section

All Automotives (All Modern Lands) (All Companies) (All Modern Lands)

HISTOPATHOLOGY INCIDENCE TABLE **RZ-75** 30 Day Sacrifice Male Rats Group L 3 3 3 3 3 3

	A N N U I M	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1										
	A E L R	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5	0 2 6	0 2 7	0 2 8										X
LYMPH NODE, POPLITEAL				X		X				<u>-</u> -	X										_{;
Pigment Deposition							••			_ 2			· - ;	·- ·-			_	-			
Lymphoid Hyperplasia							·			_ 2				-						.	- 🔀
STOMACH		X	X	Χ.	X	X	X	X	_ X	X	_ X					-	-		-		-
DUODENUM		X	X	X	X	X	X	X	X	_ X	_ X				<u>.</u>				-		 :
CECUM		X	X	X		_ X		-	X	X	X							-			
Nematodiasis					P		P				-					-	-			-	-
COLON		-	X	 X	X	X	 X	X	. X	X	X		-				• •		- •		
Nematodiasis		Р				-						-					÷		•		-
SKIN		X	X	X	_ X	. X	` X	X	X	_ X	 _ X	- ··	-		-		-				 :
TESTIS		X	- _ X	_ X	. X	_ X	_ X	_ X	. X	. X	- · X		-			-					•
EPIDIDYMIS		X	X	_ _ X	. X	. X	 X	- X	- X	- X	X				-	-					
PROSTATE		X	X	X	. X	X	X	X	X	X	X										
URINARY BLADDER	<u>.</u>	X	. X	, X	. X	X	X	. X	X	X	X		-								
	-	1	-		•																
		-																			
L		1																			•

EPL Experimental Pathology Laboratories, Inc.

P + Present N + No Section
1 + Minimar 2 + Sight
5 + Severe High 1 + Incomplete Section

CZ-75 SO Day Sacrifice Male Pats					Gr	oup	L										•		
	3	3	3	3	3	3	3	3	3	3									
A N N U I M M B	7 3 1	7 3 1	7 3 1	7 3 1	3 7 3 1	7 3 1	7 3 1	3 7 3 1	7 3 1	7 3 1									
A E L R	0 1	0 2 0	0 2	0 2 2	0 2 3	0 2	0 2 6	0 2	0 2 7	0 2									i
EMUR	 - -	X	X	X	_ <u></u> N	X	X	X	Χ	<u> </u>									 -
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RZ-75 30 Day Sacrifice Male Rats						Gr	oup	0								 	 			
	A N U I M B A E L R	3 7 3 4 - 0 1 9	3 7 3 4 - 0 2 0	3 7 3 4 - 0 2 1	3 7 3 4 - 0 2 2	3 7 3 4 - 0 2 3	3 7 3 4 - 0 2 4	3 7 3 4 - 0 2 5	3 7 3 4 - 0 2 6	3 7 3 4 - 0 2 7	3 7 3 4 - 0 2 8									22.0
LUNG]							_		_	- ,				-			_	
Accumulations of Foamy		ļ					-	-		.										
Macrophages		3_	2	2_	2	2	2	2	2	_ 2	2									
Hyperplasia of Type II Cells	5	3_	_2_	_ 2,	2	2	_ 2	. 2.	2	. 1	. 2			.						
Pigment Deposition		2_	1_	1	_ 1		_1	_ 1	1	1	1	_		_		_	-	_		
Hemorrhage		ļ						_] <u>=</u>
Edema		┨ _		_		_					_					-				
Congestion		ļ	_							-	_									
Peribronchial Lymphoid		ļ			-		-					-	_							
Hyperplasia		1	_1	. 1.	. 1	. 2		2	1	1	. 1									i
NASAL CAVITY-LEVEL I				X	_ X		X	X		X	 . X				•		-			
Hemorrhage									. 1			_		_						J.
Submucosal Pigment Deposition	on _	1	1			1		-				_								
Cystic Glands		-								-			-						-	
NASAL CAVITY-LEVEL II		-	-			-		-			-	-			-					
Hemorrhage			_						2				•		•					
Submucosal Pigment Deposition	on	2	2	2	2	2	1	1	1	1	1									-
Serous Exudate			1																	
Inflammation of Nasolacrima	1			_																-
Duct					_ 1	-			-											-
NASAL CAVITY-LEVEL III			•		-										٠					
Submucosal Pigment Depositi	on	3	3		3	3	3	3	2	3	3			•	-					
Hemorrhage	-		-				-						•		-					

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E P L Experimental Pathology Laboratories, Inc

Key P=Present 1 = Minima N = N. Section 2 = Sight $\begin{array}{lll} A = A_{\rm B}(r,y) \, c \, & \quad x = r, \ r \ {\rm April} \ {\rm and} \ c \, s \, {\rm Se} \, \epsilon \, \\ 3 = M_{\rm C} \, {\rm derafe} \, & \quad 4 \approx M_{\rm C} \, {\rm derafe} \, \, s \, {\rm Se} \, \epsilon \, \epsilon \, \\ \end{array}$

XZ-75 30 Day Sacrifice Male Rats	٢					Gr	oup	0					 					
		3 7 3 4 - 0	3 7 3 4 - 0 2	3 7 3 4 - 0 2	3 7 3 4 - 0 2	- 0 2	3 7 3 4 - 0 2	0 2	- 0 2	3 7 3 4 - 0 2	3 7 3 4 - 0 2							
HASAL CAVITY-LEVEL IV		. <u>-</u> -	0	1	2	3	4	5	6	_ 7_	8							
Submucosal Pigment Depositio Hemorrhage	ł		3.		. 4			. 1	. 1	3	3		. <u>-</u>	· - ·	-	- -	•	
YMPH NODE, TRACHEOBRONCHIAL			<u></u> -		- · — ·				-				-			•		
Lymphoid Hyperplasia Hyperplasia of Foamy		3 .	3	2	2	3	3	3	2	. 2	2		-	-			_	
Macrophages	-	4	2	. 3	. 1	4	3	3	3	3,	3	·				-		
Pigment Deposition Hemorrhage		1	1	1	1	1	1	1	. 1	1	. 1			-				
IDNEY Regenerative Tubular		-																
Epithelium	}	1	-		1	1	1		1	2								
Foci of Mononuclear Cells		1		1					. 1		1							
Casts	1	1 2	1	2	•	1	^	2	1	1 2	2							
Figment Deposition Tubular Mineralization		2	3	2	2	3	2	2	2	1	2							
ILIVER																		
Foci of Mononuclear Cells]		1						1		1							
Bile Duct Hyperplasia			1															
Focal Capsular Fibrosis																		
Pigment Deposition Hernia		•	1	1	1	1	1	1	1	1	1							

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RZ-75 30 Day Sacrifice Male Rats		<u></u>				Gr	oup	0														
	A N U I M B A E L R	3 7 3 4 - 0 1 9	3 7 3 4 - 0 2 0	3 7 3 4 - 0 2	3 7 3 4 - 0 2 2	3 7 3 4 - 0 2 3	3 7 3 4 - 0 2 4	3 7 3 4 - 0 2 5	3 7 3 4 - 0 2 6	3 7 3 4 - 0 2 7												
BRAIN		1	X	X	_ X		_ X					-		-				-				
PITUITARY		X	<u>X</u>	<u> </u>	X	 X_	_ X	X	X	. X	X					-		-			 	13.5
ADRENAL Vacuolated Cortical Cells		X	X	1	_ X	X .	X	_	1	1	_ X	- - 	- · - ·				-			-		<u></u>
EYE		<u>x</u>	X	X	- X	. X	- X	X	X	. X	X		_		•				. –			
THYROID		X	X	X	X	X	X	X	X	X	. X			-							• •	
LARYNX Foci of Mononuclear Cells	-	1	X	1		1	. 1	1	X	X	X		٠								- ·-	1.4
TRACHEA Foci of Mononuclear Cells		X	. <u>.</u> X	X	. X	X	X	X	X	, X	X			-								
HEART Monsuppurative Myocarditis	-	X		1			X	X	X	X	X										·	•
Interstitial Fibrosis SPLEEN		x	X		_ 1		X	X	X	X	: X											2
PANCREAS		x	. X	X	X	X	X	X	X	X	; x											
		1	•	·			-															
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≨2-75 ♥D Day Sacrifice Male Rats	<u></u>				Gr	oup	0				
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Å i	E	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5	0 2 6	0 2 7	0 2 8	
YMPH NODE, POPLITEAL		X	X		N	X	X	X	X	X	
Pigment Deposition	i								_		
Lymphoid Hyperplasia	•				-				-	- -	^
STOMACH	X	X	X	X	X	X	X	X	X	X	
			-						• • •		
DUODENUM	X	, X	X	X	X	X	X	X	X	X	
CECUM	X	X		X	X	X	X	X	X	X	· - · · · · · · · · · · · · · · · · · · ·
Nematodiasis			P								
JOLON	X	X	-	X	X	χ	X	X	Х	X	
Nematodiasis		-	P			-				•	
KIN	X	. X	X	X	X	X	X	X	X	X	· · · · · · · · · · · · · · · · · · ·
ESTIS	X	X	χ	X	X	X	X	X	X	X	
PIDIDYMIS	x	X	X	X	X	X	X	X	X	X	·
PROSTATE	x	X	X	X	X	X	X	X	X	X	
IRINARY BLADDER	x	X	X	X	X	X	X	X	x	X	
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RZ-75 30 Day Sacrifice Male Rats						Gr	oup	0						 					
	A N U I M B A E L R	3 7 3 4 - 0 1	3 7 3 4 - 0 2 0	3 7 3 4 - 0 2	3 7 3 4 - 0 2 2	3 7 3 4 - 0 2 3	3 7 3 4 - 0 2 4	3 7 3 4 - 0 2 5	3 7 3 4 - 0 2 6	3 7 3 4 - 0 2 7	3 7 3 4 - 0 2 8								
FEMUR			X	X	X	X				X									
ADIPOSE TISSUE		X	X	X	X	X	X	X	X	X	<u>X</u>		<u>-</u>	 - · -	- 	<u>.</u> 			
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RZ-75 30 Day Sacrifice Male Rats	Γ-					Gr	oup	М												
	M B A E A E A R	3 7 3 2 - 0 1 9	3 7 3 2 - 0 2	3 7 3 2 - 0 2	3 7 3 2 - 0 2 2	0 2	3 7 3 2 - 0 2 4	0 2	3 2	3 7 3 2 - 0 2 7	3 7 3 2 - 0 2 8				-					
LUNG		_ X								<u></u> '										
Accumulations of Foamy														-	•					
Macrophages													•	- ·			•			
Hyperplasia of Type II Cells						_				_					-		-		••	
Digment Deposition	- (·							-	•	•		٠	-
Hemorrhage							•	 1		.					-		+ .			
Edema	3							2			-	~				٠	•			
Congestion	li li							۲					-	•		-	-	* •		
Peribronchial Lymphoid							-						•				٠		-	
Hyperplasia Hyperplasia	†	•			1		1	1	1	1			-		-					
myperprasta				١.	, k	1	. 1		1	1	. ‡	•	-	-					•	
NASAL CAVITY-LEVEL I		 V	 v		 V	•	•		V	-	V						•			• •
	- 1								۸		^									
Hemorrhage Submuseral Rigment Deposition										. •										
Submucosal Pigment Depositio														•						
Cystic Glands			-	1 _	-			1				-		•						
MACAL CAVITY LEVEL 11		- .,			·	V	v	V	v	-										
NASAL CAVITY-LEVEL_II	1				. Х	. Х	X	, Х	λ		X									
Hemorrhage						-				2										
Submucosal Pigment Depositio	n	-			-															
Serous Exudate	j	-																		
Inflammation of Nasolacrimal	1						ē													
Duct	ł	-																		
NASAL CAVITY-LEVEL III	}																			
	1	X	X	N	X	X	X	X	X		X									
Submucosai Pigment Depositio	n																			
Hemorrhage	1									3										

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EPL

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Key Parracet Nett Solling
1=Nora 2=Sight
6=Sight 1 to company So

R2-75 30 Day Sacrifice Male Rats				<u>. </u>		Gr	oup	M		-								 		
	A N U I M B A E L R	3 7 3 2 - 0 1 9	3 7 3 2 - 0 2 0	3 7 3 2 - 0 2	3732-022	3 7 3 2 - 0 2 3	3 7 3 2 0 2 4	3 7 3 2 - 0 2 5	3 7 3 2 - 0 2 6	3 2 -	3 7 3 2 0 2 8									
NASAL CAVITY-LEVEL IV		X	X		X	X	X	X	X	Х	X					_				
Submucosal Pigment Depositio	<u>n</u>			<u>-</u>						<u>.</u> .									-	
Hemorrhage				2									-						-	
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EPL

Experimental Pathology Laboratories, Inc.

Key P = Present

Z-75 30 Day Sacrifice Male Rats					·-··	Gr	oup	N —												
	A N U I M M B A E L R	3 7 3 3 - 0	3 7 3 3 - 0 2	3 7 3 3 - 0 2	3 7 3 3 - 0 2	_		3 7 3 3 0 2		3 7 3 3 - 0 2	3 7 3 3 - 0 2									
UNG		9 X	0	1	_2_	_3_	4_	5	_6_	_1_	_8									
Accumulations of Foamy											-							-	-	•
Macrophages							1	1			_	_					-			
Hyperplasia of Type II Cells	.					· · · · <u> </u>	1	1		<u>.</u> .				_	_				•	
Pigment Deposition							1	1	-											,
Hemorrhage		 			•	- -					_					-				
. Edema						 -			-		-									
Congestion		 						-				-		-						
Peribronchial Lymphoid	· ··							-								-				
<u>Hyperplasia</u>			1	1	. 1	1	1	1	. 1	1	1				-		-			
ASAL CAVITY-LEVEL I Hemorrhage		•			- X	X	X	, X	X	X	X					=				
Submucosal Pigment Deposition Cystic Glands)rī				-	-				•	-	•		٠	-					
Cystic Stands	••	1	•	*	-	•						•	•							
ASAL CAVITY-LEVEL II Hemorrhage		x			X	, X	X	X	, X	` X	X		•							
Submucosal Pigment Deposition	חכ			1																
Serous Exudate Inflammation of Nasolacrima Duct	 I																			
ASAL CAVITY-LEVEL 111		X			X				X	X										
Submucosal Pigment Deposition	on		. 1	1		1	1	1			1									
Hemorrhage				-																

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GROUP	DOSE (mg/m3)	TREATMENT
L	0	Controls
M	1	Low Exposure Concentration
N	10	Medium Exposure Concentration
0	100	High Exposure Concentration

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₹2-75 30 Day Sacrifice Male Rats					~	Gr	oup	N N				 		· _ · - ·					·
	A N U I M B A E L R	3 7 3 3 - 0 1 9	3 7 3 3 - 0 2 0	3 7 3 3 - 0 2	3 7 3 3 - 0 2 2	3 7 3 3 - 0 2 3	0	3 7 3 3 - 0 2 5	3 7 3 3 0 2 6	3 7 3 3 - 0 2 7	3 7 3 3 0 2 8								
HASAL CAVITY-LEVEL IV		1	_ <u>-</u> _	_ <u>+</u> _	<u></u> X				<u>o_</u> X	<u> </u>	- · - -	 							
Submucosal Pigment Deposition Hemorrhage	on		. :· 		- `` -	-	1	_ _ 1		.^^ 	· ·	 -	2		-	-			· · · · · · · ·
YMPH NODE, TRACHEOBRONCHIAL Lymphoid Hyperplasia		1							X		. X	 - 					_		
Hyperplasia of Foamy Macrophages	 			· -				-	- -		-		-	-			<u>-</u>	. _	_
Pigment Deposition Hemorrhage			<u>-</u>									-							-
IDNEY Regenerative Tubular	 		<u>-</u> 		-		-		-								•		
Epithelium Foci of Mononuclear Cells Casts		-	_ 2 _ 1 _ 1	, 1 -	. 1	1	-	. 1	- . 1	. 1		-				•			
Pigment DepositionTubular Mineralization		1	_ 1 	. 1	1	1	. 1	1	. 1	1	1								
LIVER	-		_ X		X	X		X											
Foci of Mononuclear Cells Bile Duct Hyperplasia							. 1		1	1	1								
Focal Capsular Fibrosis Pigment Deposition Hernia																			
	-			-															

RZ-75 30 Day Sacrifice Female Rats Group L 7 M B A E | -LUNG Accumulations of Foamy Macrophages Hyperplasia of Type II Cells Pigment Deposition Hemorrhage Edema Congestion Peribronchial Lymphoid Hyperplasia 1 1 NASAL CAVITY-LEVEL I X X X X X X X X X X Hemorrhage Submucosal Pigment Deposition Cystic Glands NASAL CAVITY-LEVEL II Hemorrhage Submucosal Pigment Deposition Serous Exudate Inflammation of Nasolacrimal Duct 2 NASAL CAVITY-LEVEL III Submucosal Pigment Deposition Hemorrhage ____

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RZ-75 30 Day Sacrifice Female Rats					G 	rou	р L														
C C C C C C C C C C C C C C C C C C C	A N N U I M N B	3 3 1	3 7 3 1																		
	A E L R	5 1 9	5 2 0	5 2 1	5 2 2	5 2 3	5 2 4	5 2 5	5 2 6	5 2 7											
NASAL CAVITY-LEVEL IV		X	X	X		X	X		X	X											
Submucosal Pigment Deposition	1														·				-	•	
Hemorrhage									· 	_							_				
																_					
LYMPH NODE, TRACHEOBRONCHIAL		X	X	X	X	X	N	Ņ	_ X	X								_			_
Lymphoid Hyperplasia												_				_			_		
Hyperplasia of Foamy							-				_		_	_							
Macrophages		.								-									-		
Pigment Deposition				-													-		÷	-	-
Hemorrhage						-		-						-		-				-	<u>. </u>
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KIDNEY			-																		-
Regenerative Tubular																					
<u>Epithelium</u>						÷	-			,	-	•	•	÷	·						
Foci of Mononuclear Cells		-	-		-		-			-							-				-
Casts																					
1		1	_ 1	1	1	1	1	1	1	ì				٠							
Tubular Mineralization			-	-	•				•					•							
LIVER			X		٧		X		X												
Foci of Mononuclear Cells		,	. ^	1	. X	1	. ^	1	^												
Bile Duct Hyperplasia		•		. •		•		•		1											
Focal Capsular Fibrosis		ļ		•	•					•											
, Pigment Deposition			-	-	•																
Hernia	-		-												٠						
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RZ-75 30 Day Sacrifice Female Rats					(ŝroi	ap L					<u></u>			 		 		
	A N N U I M M B	3 7 3 1	3 7 3 1	3 7 3 1		3 7 3 1		3 7 3 1	3 7 3 1	3 7 3 1									
·	A E L R	5	5 2 0	5 2 1	5 2 2	5 2 3	5 2 4	5 2 5	5 2	5 2 7									
BRAIN		X.	X	X			. X	X	X	X					 				
PITUITARY		X.	X	- , X	_ X	X	X	X	X	. X		-		-	 •	-		- 	F .
ADRENAL Vacuolated Cortical Cells		1					X	X	X	X	-	-	*						
EYE	· · · ·	X	_ X	, ,	X	 X	, X	X	X	, X							•	-, •	
THYROID	. 	x	 X	 X	X	X	X	, X	X	X		-					٠		
LARYNX		1				X		1	X	X									,,,
TRACHEA		X	X	. X	 . X	X	. X		X	X		-						!	•
Foci of Mononuclear Cells		 						1						-					
HEART Nonsuppurative Myocarditis Interstitial Fibrosis		X	, X	, X	, X	X	, ,	X	X	X								•	
SPLEEN		X	X	X	X	X	X	X	X	X									_
PANCREAS		X	X	X	X	X	X	X	X	X								•	•
				-														1	
		1			-										 		 		

twlZ-75 130 Day Sacrifice Female Rats				G	irou	p L						 	 _		. .	
A M N L I N M E A E L F	3 1 -	3 7 3 1 - 5 2 0	3 7 3 1 - 5 2 1	3 7 3 1 - 5 2 2	3 7 3 1 - 5 2 3	3 7 3 1 - 5 2 4	3 7 3 1 - 5 2 5	3 7 3 1 - 5 2 6	3 7 3 1 - 5 2 7				 			
YMPH NODE, POPLITEAL Pigment Deposition Lymphoid Hyperplasia	X	<u>X</u>	X	, X	X	X	X	X	X		<u>-</u>	-	-	-		
STOMACH	. X		. X	X	X	 - X	X	. X	X _		•	-	-	-		- -
DUODENUM	X	X	X	X	X	X	X	X	. X .		,					
CECUM Nematodiasis	X	, X	X	X	. X	X	X	X	Χ.							
COLUN	X	` X	P	X	X	X	X	P	X							-
SKIN	N	X	N	, X	N	X	X	X	X							
Parovarian Cyst	x	. P	P		X	X	X	X	X		-					
UTERUS	x	-	, X	X	X	, X		X	X	÷						
URINARY_BLADDER	X	, N	X	X	X	X	X	X	X							
				•	•											

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RZ-75 30 Day Sacrifice Female Rats		•		G	rou	ıp L		_							 		
A N N U I M M B A E L R	3 7 3 1 - 5	3 7 3 1 - 5	3 7 3 1 - 5	3 7 3 1 - 5 2	3 7 3 1 - 5 2	3 7 3 1 - 5	3 7 3 1 - 5	3 7 3 1 - 5	3 7 3 1 - 5								328 EV
FEMUR	1 9 v	2 V	2 1 v	2_	_3_	2 4 v	2 5 v	2 6 v	2 7 X				 	 			
1 Ellon	^	Δ	_^	X	^	. ^	. ^	. ^	^								77.
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Kry Perbinant New Solice
1 - Morta 2 = Soft
5 - Solice Hot Central Control

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RZ-75 '30 Day Sacrifice Female Rats	ſ				Gr	oup	0										 -			
A N N U I M M B A E L R	3 7 3 4 - 5 1 9	3 7 3 4 - 5 2 0	3 7 3 4 - 5 2	3 7 3 4 - 5 2	3 7 3 4 - 5 2 3	3 7 3 4 - 5 2 4	3 7 3 4 - 5 2 5	3 7 3 4 - 5 2 6	3 7 3 4 - 5 2 7	3 7 3 4 - 5 2 8										
LUNG													_							
Accumulations of Foamy	1		•••	~-		-				•	•			-		_		~	•	
Macrophages	2	3	2	2	2	2	3	2	2	_ 2			•		• •	-			•	
	2				2	2	2	2	2	2	•					•				
Pigment Deposition	1	1	1	1	1	1	1	1	1	1										
Hemorrhage		• •		-		-						•		•	•			•		
Edema	1	~		•						•		•			٠		-			•
Congestion	1	-							-					•						•
Peribronchial Lymphoid			-						•			•			•					
Hyperplasia	1	1	1	1	2	1	2	2	1	1		·								
NASAL CAVITY-LEVEL I Hemorrhage		. X	X		X			X	N											
Submucosal Pigment Deposition Cystic Glands	1		-	1		1	1			_ 1	-									-
NASAL CAVITY-LEVEL II Hemorrhage								-	N	•										
Submucosal Pigment Deposition Serous Exudate	1	1	1	2	1	2	1	1		1										
Inflammation of Nasolacrimal Duct			-	٠																
NASAL CAVITY-LEVEL III Submucosal Pigment Deposition Hemorrhage	2	3	2	3	3	3	2	3	N	2			-							

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Key P = Present N = N Section A = A, r = N N to attend to the constitution of the Present N = Section 3 = M to attend to the constitution of the present N = N Section 3 = M to attend to the constitution of the present N = N Section N = N to attend to the present N = N Section N =

RZ-75 30 Day Sacrifice Group O Female Rats NASAL CAVITY-LEVEL IV X N Submucosal Pigment Deposition 3 1 1 2 1 1 3 2 Hemorrhage LYMPH_NODE, TRACHEOBRONCHIAL _____ Hyperplasia of Foamy 3 2 3 2 2 3 3 2 3 2 . _ Macrophages____ Pigment Deposition 1 1 1 1 1 1 1 1 1 1 1 <u>H</u>emorrhage KIDNEY Regenerative Tubular __Epithelium_____1 Foci of Mononuclear Cells 1 Casts 2 2 2 2 2 2 2 2 2 2 Pigment Deposition Tubular Mineralization LIVER _____ Foci of Mononuclear Cells Bile Duct Hyperplasia Focal Capsular Fibrosis Pigment Deposition_ 1 1 1 1 1 1 1 1 1 1 Hernia

V-21

EPL

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₹2-75 ₹30 Day Sacrifice Female Rats		_				Gr	oup	0												
	A N U I M B A E L R	3 7 3 4 - 5 1	3 7 3 4 - 5 2	3 7 3 4 - 5 2	3 7 3 4 - 5 2	3 7 3 4 - 5 2	3 7 3 4 - 5 2	3 7 3 4 - 5 2	3 7 3 4 - 5 2	3 7 3 4 - 5 2	3 7 3 4 - 5 2									
		9	0	1	2	3	4	_5_	6	7	8									
3RAIN	<u>.</u>	Ϋ́	. X .	X	X	. X	Ϋ́	У.	X	N	. X	-				-				
PITUITARY		X	_ X	 X	X	X	. X	X	X	N.	_ X .						-			
ADRENAL		 X	X	. X		 X	X	 X	 X	X	_ X	-						-	-	
Yacuolated Cortical Cells			. °				· ''	-		•						-	٠			
EYE	-	X	 X	X	X	 X	X	. <u>.</u>	X	N	X	-				•				
			-			-	•		•		•		-		-	-	-			
THYROID		X	. X	X	χ.	X	X	. X	X	X	X			-	-					- —
LARYNX Foci of Mononuclear Cells		X	X	X	X	X	X	X	X	X	X		-		٠			·		. –
TRACHEA Foci of Mononuclear Cells		X	, X	X	. X	X	X	X	X	. X	X									-
HEART Nonsuppurative Myocarditis		x	. X	X	X	N	X	X	X	X	1									
Interstitial Fibrosis						•														
SPLEEN		X	X	X	X	X	, X	X	X	X	X									
PANCREAS		X	, X	X	X	, X	X	X	X	X	X									
		1	·				-													

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E P L

Experimental Pathology Laboratories, Inc

RZ-75 30 Day Sacrifice Female Rats		<u></u>				Gr	oup	0				-		_	 					
	A N N U I M M B A E L R	3 7 3 4 - 5 1 9	3 7 3 4 - 5 2	3 7 3 4 - 5 2	3 7 3 4 - 5 2	3 7 3 4 - 5 2 3	3 7 3 4 - 5 2 4	3 7 3 4 - 5 2 5	3 7 3 4 - 5 2 6	3 7 3 4 - 5 2 7	3 7 3 4 - 5 2 8									
LYMPH NODE, POPLITEAL		1			X	X	X	. X	X	X	_ X				 -	•				
Pigment Deposition Lymphoid Hyperplasia		1					-				- ·						-	-	-	1
STOMACH	· · ·	X	X	_ X	. X	X	X	X	- , X	X	- <u>-</u> X	-	-	-				-	-	
DUODENUM		X	. X	X	X	X	. X	X	X	X	X		•	-					-· ·	
CECUM Nematodiasis	 	X	X	, X	X	X	P	X	X	X	P									
COLON _Nematodiasis	·	P	_ X	X	X	X	X	X	X	X	P				٠					
SKIN		X	X	X	X	X	X	X	X	X	. x		÷							
OVARY Parovarian Cyst	•	X	_ X	X	X	X	X	X	P	X	X									
UTERUS		Y	- Y			X	Y	¥	¥	Y	¥									
Dilatation		1	. ^		2	^	^		^	^	^									1,
URINARY BLADDER		X	X	X	X	X	X	X	X	X	X									
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ey P + Present N + Nr Section
1 + Mr. ma 2 + Silgri
5 + Suvere High 1 + Incomplete Section

₹2Z-75 ₹30 Day Sacrifice Female Rats	1					Gr	oup	0					 	 		 	
	A N U I M B	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4	3 7 3 4						:
	M B A E L R	5 1 9	5 2 0	5 2 1	5 2 2	5 2 3	5 2 4	5 2 5	5 2 6	5 2 7	5 2 8						
EMUR		X	X	X	X	X	X	X	X	X	X						
ADIPOSE TISSUE		X		X	. <u>X</u>	X	X	X	X	. X	X						
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Key Piesent Nie 1 = Minimat 2 + 5 = Severe High 1 =

N=Nr Section 2 + Slumb 1 = n - riplete Secto A + A in year in A in the remarkation 2 + M in the At in M in the Visitoria M

RZ-75 30 Day Sacrifice Female Rats

Group M

Female Rats												 								 1
	A N N U I M M B A E L R	3 7 3 2 - 5 1 9	3 7 3 2 - 5 2	3 7 3 2 - 5 2	3 7 3 2 - 5 2	3 7 3 2 - 5 2 3					3 7 3 2 - 5 2 8									
LUNG						_ <u></u>	X	X	X								-			
Accumulations of Foamy					 .			-			-					-				
Hyperplasia of Type II Cells		1														-	٠	-		 1
Pigment Deposition		i i											-	-	-	•			•	
Hemorrhage		ł																		
Edema		!		•		-								_						
Congestion		ı						_		1	-	 -	•							 ļ
Peribronchial Lymphoid											-									
Hyperplasia			1	1	1					1	1		-	w						
NASAL_CAYITY-LEVEL_I Hemorrhage Submucosal Pigment Deposition Cystic Glands			- • ·			. X	X -	X	X	X	X					-				
NASAL CAVITY-LEVEL II Hemorrhage Submucosal Pigment Depositi Serous Exudate Inflammation of Nasolacrima Duct			X		X	X	X	X	X	X	X									
NASAL CAVITY-LEVEL III Submucosal Pigment Depositi Hemorrhage	on	X	X	X	X	X	N	X	X	X	X			-						

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Key P = Piesei

N = No Section
2 = Slaht

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RZ-75 30 Day Sacrifice Female Rats	_					Gr	oup	М											
AN - MAI	N U M B E R	3 7 3 2 - 5 1 9	3 7 3 2 - 5 2 0	3 7 3 2 - 5 2 1	3 7 3 2 - 5 2 2	3 7 3 2 - 5 2 3	3 7 3 2 - 5 2 4	3 7 3 2 - 5 2 5	3 7 3 2 - 5 2 6	3 7 3 2 - 5 2 7	3 7 3 2 - 5 2 8								
JASAL CAVITY-LEVEL IV		X	X	X	X	Χ	X	X	X	X	X								
Submucosal Pigment Deposition				-					.						_				
Hemorrhage		_												-					
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Key P. Prosent N=Nr Section
1 M ma 2=Sight
5 Sivice High 1 = incomplete Sector

RZ-75 30 Day Sacrifice Female Rats	ſ					Gr	oup	N					 	_		
	N N U M B N E R	3 7 3 3 - 5 1 9	3 7 3 3 - 5 2 0	3 7 3 3 - 5 2	2	3 7 3 - 5 2 3	- 5 2	5 2	- 5 2	- 5 2	5 2					
LUNG																_
Accumulations of Foamy Macrophages Hyperplasia of Type II Cells										_			 			
<u> Macrophages</u>								. 1	. 1					-		
"Maciniagia of The infection			-						±	-						-
Pigment Deposition Hemorrhage					, . <u>-</u> .			. 1	1	_		<u>-</u> .				_
Hemorrhage		-				_	. .	-							_	. <u>.</u> .
Edema																
Congestion																
Peribronchial Lymphoid																
Hyperplasia	-	1	1	1	1	1	1	1	1	1	. 1					
NASAL CAVITY-LEVEL I							X	X	X	X	X					
Submucosal Pigment Deposition																
_Cystic Glands					_					_						
		_	-						_	<u>.</u>	_					
NASAL CAVITY-LEVEL II Hemorrhage	_															
Submucosal Pigment Deposition Serous Exudate	١	-		1												
Inflammation of Nasolacrimal Duct																
NASAL CAVITY-LEVEL III Submucosal Pigment Deposition Hemorrhage	n]		X	1	. X	X		1		X	N	l				

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EPL

Key P+Present N=N: Section
1+Minma 2+5-ght

Autoposition to the majoration Miliated 4 - Miliated Southers

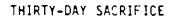
RZ-75 30 Day Sacrifice Female Rats	-	-,				Gr	oup	N —-					_		 				
								_	_		_								
A N	N U M B E R	3 7 3 3 - 5 1 9	3 7 3 3 - 5 2 0	3 7 3 3 - 5 2	3 7 3 3 - 5 2 2	3 7 3 3 - 5 2 3	3 7 3 3 - 5 2 4	3 7 3 3 - 5 2 5	3 7 3 3 - 5 2 6	3 7 3 5 - 5 2 7	3 7 3 - 5 2 8								
HASAL CAVITY-LEVEL IV		3	<u> </u>	1	X	_ X	X		<u> </u>		⊻				 				
Submucosal Pigment Deposition Hemorrhage		1		1		-	-	1	. 1	1	1			·			-		-
		v	-	v	v	v			v	v	M		-		-				
YMPH NODE, TRACHEOBRONCHIAL	-	X	X	X	. X	X		. ^	٨	X	, N					•			
Lymphoid Hyperplasia	1										-						-	•	-
Hyperplasia of Foamy Macrophages	-										-	-							-
Pigment Deposition			-			•			-			-			-		-		-
Hemorrhage			•				1												
			_																
LIDNEY									X		X								
Regenerative Tubular			_																
Epithelium							1	1											
Foci of Mononuclear Cells		1		1															
Casts																			
Pigment Deposition		1	1	1	1	1		1		1									
Tubular_Mineralization	,																		
 €																			
LIVER				X	X		X	X	X	X	X								
Foci of Mononuclear Cells		1	1																
Bile Duct Hyperplasia		-				1													
Focal Capsular Fibrosis																			
Pigment Deposition																			
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Experimental Pathology Laboratories, Inc

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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS TABLES

CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

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Group Number L - Sacrificed

Sex Males

Species Rats

Dosage Level 0 mg/m³

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Microscopic Observations	Lymphoid hyperplasia; pigment deposition														
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Clent's Gross Observations		; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ; ;		-		:		l i	i			:	: !	: !	' i
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J	Popliteal lymph node							: ! !	i İ				<u> </u>	· ·	: : !
Animal	3731-027			 		† !	† ·- 	{ - ·· } 	† į		: 	 	.		!
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CORRELATION OF GROSS AND MICROSCUPIC FINDINGS

Group Number 0 - Sacrificed

Sex Males

Species Rats

Dosage Level $100~\text{mg/m}^3$

Microscopic Observations	Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition	Lymphoid hyperplasia; pigment deposition Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding lesion (adipose tissue) Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding lesion (adipose tissue) Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	Nó córresponding leston tadipose tissue)	
Client's Gross Observations	Dark, moderate, enlarged	Gray Diffuse mild gray color	Green/gray Enlarged, mild, dark	Diffuse, moderate, gray	Moderate, gray/green Enlarged, mild, dark	Diffuse, moderate, gray	Gray/green	Green/gray color
Chent's Tissue Identification	Tracheobronchial lymph node	Popliteal lymph node	80dy fat 3734-020 Tracheobronchial lymph node		Fat Tracheobronchial lymph node	Lung	Fat	Body fat
Anmal	3734-019		3734-020		3734-021			[_3734-022] Body fat

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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Species Rats

Sex Males

Group Number 0 - Sacrificed

Dosage Level 100 mg/m³

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Microscopic Observations	Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition	Pigment deposition Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding lesion (adipose tissue) Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding leston (adipose tissue) Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition
Chent's Gross Observations	Enlarged, mild, dark	Gray Diffuse, mild-moderate, gray	Enlarged, mild, dark	Diffuse, moderate, gray	Green/gray Enlarged, mild, dark_	Diffuse, moderate, gray	Green/gray Enlarged, mild, dark
Client's Tissue Identitication	Tracheobronchial_lymph_node	Popliteal lymph node	3734-023 Trackeobronchial lymph node	Lung	FatTracheobronchial lymph node		Fat Tracheobronchial lymph node
Anmal	3734-022 (Cont'd)		3734-023		3734-024		3734-025

Dosage Level 100 mg/m³	Microscopic Observations	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding lesion (adipose tissue) Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding lesion (adipose tissue) Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment_deposition	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition	No corresponding lesion (adipose tissue) Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition
Group Number 0 - Sacrificed	Client's Gross Observations	Diffuse,_moderate, gray	Green/gray	Diffuse, mild-moderate, gray	Green/gray Dark, mild enlarged	Diffuse, mild-moderate, gray	Green/gray Enlarged, moderate, dark	Diffuse, moderate, gray
Rats Sex Males G	Chent's Tissue Identification	S Lung	Fat6			Lung	3734-028, Tracheobronchial lymph node	L Lung
Species Ra	Animal	3734-025 (Cont'd)	3734-026		3734-02		3734-02	

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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

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Dosage Level 1 mg/m³	Microscopic Observations	No corresponding lesion	Hemorrhage	No corresponding lesion				
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Group Number M - Sacrificed	Chent's Gross Observations	Moderate redness	Moderate redness Dark redness Dark red and shiney throughout bloody froth from trachea	Oull pinkish gray +2				VI-6
Sex Males	Client's Tissue Identification	Lung	Lung	Lung				
Species Rats	Anmal Nur ber	3732-020 Lung	3/32-023 Lung 3/32-024 Lung 3/32-025 Lung	3732-028 Lung				

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CORRELATION OF GROSS AND MICROSCOPIC FINDINGS

Group Number N - Sacrificed Males Sex Rats Species

Dosage Level 10 mg/m³

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Anmal Number	Clent's Tissue Identification	Client's Gross Observations	Microscopic Observations
3733-019	Lung	Diffuse gray coloring	No corresponding lesion
3733-020	Lung	Gray_diffuse_areas	No_corresponding leston
3733-021	Lung	Grayish tan colored areas	No corresponding lesion
3733-022	Lung	Diffuse gray/brown color	No_corresponding_lesion
3733-023 Lung	Lung	Brownish green patchy discoloration	No corresponding lesion
3733-024 Lung	Lung	Gray diffuse areas	pigment deposition; hyperplasia of type II cells
3733-025	Lung	Grayish brown areas with moderate redness	Accumulations of foamy macrophages; pigment deposition; hyperplasia of type II cells
3733-026 Lung		Diffuse mild gray coloring	No corresponding leston
3733-027 Lung	Lung	Gray diffuse colored areas	No corresponding lesion
3733-028 Lung	Lung	Grayish brown colored areas	No corresponding leston

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COPRELATION OF GROSS AND MICROSCOPIC FINDINGS

Group Number 0 - Sacrificed

Sex Females

Species Rats

Dosage Level 100 mg/m³

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Animal	Client's Tissue Identification	Client's Gross Observations	Microscopic Observations
3734-519	Tracheobronchial lymph node	Enlarged, moderate, dark	Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition
	Lung	Diffuse, gray, moderate	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition
3734-520	Fat Tracheobronchial lymph node	Gray/green Enlarged, moderate, dark	No corresponding lesion (adipose tissue) Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition
	Lung	Diffuse, gray	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition
3734-521	Tracheobronchial lymph node	Enlarged, mild, black	Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition
	Lung	Diffuse, moderate, gray	Accumulations of foamy macrophages; hyperplasia of type II cells; pigment deposition
3734-522	Fat Tracheobronchial lymph node	Green/grayEnlarged, mild, dark	No corresponding lesion (adipose tissue) Lymphoid hyperplasia; hyperplasia of foamy macrophages; pigment deposition
	Fat	Green/gray	No corresponding lesion (adipose tissue)

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